Sleep Induced Peaks in Intraocular Pressure and Possible Implications with the use of Prostaglandin Analogue Drugs in the Management of Chronic Open Angle Glaucoma.

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ABSTRACT

The exact nature of the circadian rhythm for intraocular pressure is still open to debate, some authors suggesting that peak episodes occur during the day while others have presented evidence suggesting tension spikes during sleep. It has also been suggested that pressure peaks are potentially more damaging than mean or daytime pressures. If this is correct, and if pressure peaks are more likely to occur outside office hours it would be clinically significant if a predicable pattern could be identified; medical treatment being tailored to target the most damaging tension epochs. This could be particularly important with the introduction of prostaglandin analogue drugs requiring once daily instillation.

Intraocular pressure was recorded in 25 non-glaucomatous volunteers (mean age 21 - range 10 to 53) over a continuous 24-hour period. Tension spikes were found in all subjects while in 'deep' sleep, regardless of the time of day. Subjects who could not sleep or had sleep depths graded as 'light' did not demonstrate the IOP spikes.

Prostaglandin analogues are licensed for even instillation. A more specific time is not stipulated. Generally this would appear to be the most appropriate time for habitual, nocturnal sleep patterns, but stipulating early evening specifically would ensure maximal drug effect coincides with maximum tension.

Word length (body of text – 13,500).

CONTENTS

LITERATURE DECLARATION

With the exception of three references, copies of all literature cited in this paper are held by the author and can be supplied on request.

The exceptions are :

Elliott D.B. (1998). Contrast sensitivity and glare testing. In Benjamin W.J. (ed) *Borish's Clinical Refraction*. Orlando. WB Saunders.

Pickering TG. (1991). *Ambulatory Monitoring and Blood Pressure Variability.* Science Press. London.

Shields MB. (1982). *A Study guide for Glaucoma*. Baltimore. Williams and Wilkins.

INTRODUCTION

Terminology of Cyclic Rhythms.

The existence of a regular, phasic variation in intraocular pressure throughout the 24-hour period in both normal and glaucomatous eyes is well documented and accepted. Many papers describe a 24-hour rhythm as diurnal in nature (Henkind, Leitman & Weitzman 1973, Kitazawa & Horie 1975, Henkind & Walsh 1981, Frampton, Da Rin & Brown 1987, Wildsoet, Brown & Swann 1990, Ido, Tomita & Kitazawa 1991, Wilensky 1991, Pointer 1999). The term 'Diurnal' specifically pertains to the daylight portion of the 24-hour period and is the opposite of 'nocturnal', which refers to the dark portion of the 24-hour period. Racz, Ruzsonyi, Nagy, Gagyi & Bito (1996) use the terms diurnal and nocturnal in their accurate senses. A more appropriate term for a 24-hour cycle is 'Circadian' meaning 'being, having, characterized by, or occurring in approximately 24 hour periods or cycles' and further is 'independent of environmental variation'. Circadian does imply a cyclic rhythm while nyctohemeral simply designates a 24-hour period (Appendix 1 – Definitions of 'Circadian', 'Diurnal' and 'Nocturnal').

In this paper the terms 'Nocturnal' and 'Diurnal' will only be used if specifically referring to night-time or daytime, respectively. When considering habitual 24-hour rhythms the term 'circadian' is used and nyctohemeral is reserved for 24-hour periods without any inference of a defined rhythm.

A 'sleep/wake' cycle is also referred to, as distinct from a circadian one, since it is postulated that sleep induces IOP changes independently of any habitual circadian variations.

Relevance of Intraocular Pressure Variations – peaks versus means.

While a circadian curve is accepted, its' exact nature is still questionable. In the textbook 'The Glaucomas', Zeimer (1996) quotes the paper by Katavisto (1964) as suggesting we should consider four general types,

1) morning peak,
2) daytime peak,
3) night type peak,
4) flat.

The fact that this paper is still emphasised in a current textbook after 40 years demonstrates that, if a characteristic circadian cycle exists at all, a concise understanding of it does not.

Diagnostically the exact timing and magnitude of IOP peaks is less important, especially in view of the prevalence of normal tension glaucoma within the glaucomatous population (Werner 1996). Optometrists rely on other clinical techniques such as disc assessment and photography, fields and scanning laser polarimetry for glaucoma detection and referral specificity and sensitivity.

While not necessarily of critical diagnostic value, Gelatt and MacKay (2001) remark that daily spikes in IOP may be important in the management of glaucoma since they potentially cause the most damage.

There is still some discussion as to what does constitute the highest risk for glaucoma progression. Gelatt and MacKay (2001), Kontas, Maltezos, Gandi, Hudgins and Stewart (1999) and Zeimer, Wilensky and Gieser (1990) suggest that, intuitively, IOP peaks should be significant. Kontas and co workers further suggest that the timing of a patient's personal IOP peak, if it could be ascertained, could be an important factor in timing drug administration.
Smith (1985) assessing ranges of IOP, diurnal variation and timing of peaks and troughs could not find a significant correlation between any of the variables and progression of field loss. Smith only measured IOP between 5am and 3pm

because this is when the author expected peaks to occur. This assumption was based on cited literature for that time, but meant that any nocturnal variability would not be sampled.

Zeimer, Wilensky, Gieser and Viana (1991), using the 'self tonometer', sampled tensions at waking, noon, 4.00pm, dinner and bedtime. These authors acknowledge that the limited number of sample times would reduce the sensitivity of the procedure but did find that progression of field loss was correlated to the magnitude and number of pressure peaks. Like Smith, these researchers tried to target measurement times to sample the potentially highest pressures. The 'on waking' measurement is particularly critical and its' inclusion is undoubtedly as a consequence of the IOP spike on waking, reported by Zeimer *et al* (1990). The authors include a cautionary note to the interpretation of these results. Just as elevated IOP measured in the clinic is not pathognomonic for glaucoma, episodic IOP spikes may be an equally vague index for the prediction of progressive field loss.

Asrani, Zeimer, Wilensky, Gieser, Vitale and Lindenmuth (2000) were far more specific about the level of risk that fluctuations in IOP pose for the patient. These authors found that large fluctuations in IOP during the day have an effect over and above any other known risk factors for visual field progression.

If daily IOP spikes exist, and if it is accepted that IOP peaks are more important in predicting glaucomatous damage than mean IOP or ranges in IOP, drug efficacy would be enhanced if the instillation could be timed for maximal effect coinciding with the IOP peak. This fact is of particular salience with the emergence of prostaglandin analogue drugs requiring once daily instillation.

The aim of this paper therefore, is to try to ascertain if predictable tension peaks exist and if they do how could this affect the prescribing modality of prostaglandin analogues.

Conflicting Paradigms of IOP Circadian Variations

Since the first mention of the existence of circadian variations in intraocular pressure by Maslenikow in 1904 (Duke-Elder 1952) a plethora of papers have been published on the subject. Conflicts in the results may largely mirror differences in methodology and instrumentation.

Duke-Elder (1952) describes three types of curve. Type 1 patients show heightened IOP on waking, peaking soon after, followed by a gradual fall. Type 2 curves trough in the morning and then climb to a peak in the late afternoon, while Type 3 rises through the morning to peak about 10.00am, falls to a trough and rises again to a second peak around 6pm. In these experiments pressures were recorded with Schiotz and no measurements were made between midnight and 5.00am while the patients slept.

Ericson (1958), reports a general understanding at the time that pressure drops during the day and rises at night with a peak about 4.00am. His experiment was striving to monitor circadian changes in aqueous humour influx. By eliminating other variables with ocular suction cups he estimated aqueous humour inflow variations as a function of intraocular pressure changes. This author found an IOP minimum at 4.00am.

Henkind *et al* (1973) recorded tension throughout the 24-hour period with a Mackay-Marg tonometer. They recorded a pressure minimum at about 3.00am. These results were supported by the work of Henkind and Walsh (1981), who also suggested a sleep/wake cycle. As in the earlier work, tensions were recorded hourly over the nyctohemeral period using a Mackay-Marg tonometer. The patient was placed in a supine position for five minutes prior to readings. No time delays were recorded before readings during the sleep periods, where presumably the patients were already supine.

The existence of a night-time pressure trough was further championed by Kitazawa and Horie (1975). Tensions were recorded using Goldman tonometry

hourly over 24 hours. An IOP minimum was suggested to be between 1.00 and 5.00am.

Frampton and co workers (1987) using an AO non-contact tonometer found a significant sleep induced rise in IOP. During the sleep cycle the subjects still needed to rise to have tensions recorded. However, no anaesthesia was required and the proximity of the tonometer enabled all readings to be taken within several minutes of waking. An extension of the same research indicated that the rise was sleep rather than posture or darkness induced and further showed that the intraocular pressure rise could not be attributed to closed lid induced corneal oedema during sleep.

Frampton *et al* (1987) and Brown, Burton, Mann and Parisi (1988b) also demonstrated a very rapid return to normal pressure after waking; near normal tensions being achieved within three minutes of waking.

Zeimer *et al* (1990), while not recording diurnal variation, also noted a significant IOP peak at waking followed by a rapid drop within half an hour. The instrument used in these trials was the 'Self Tonometer' described in detail in Wilensky, Gieser, Mori, Langenberg and Zeimer (1987) and designed specifically as a means of monitoring tensions outside office hours. Zeimer and associates reported their findings as significant because the same patients had pressures well within normal limits when recorded during office hours.

Wildsoet *et al* (1990) using a Reichart NCT, Wildsoet, Eyeson-Annan, Brown, Swann and Fletcher (1993) and Birchley, Mudie and Brown (1990) using Keeler pulsair non-contact tonometers and Buguet, Py and Romanet (1994) using a tonopen presented further data supporting sleep induced tension peaks. The Reichart and Keeler non-contact tonometers are used without anaesthetic, and patients can remain supine with the Keeler. While anaesthetic is required for the tonopen the patients were able to remain recumbent which minimised sleep disruption and measurement delays.

Birchely *et al* (1990) and Buguet *et al* (1994), further, were able to quantify sleep levels using polygraphic techniques. Prior to these studies, either no assessment of sleep depth was possible or was not considered.

Liu, Kripke, Hoffman, Twa, Loving, Rex, Gupta and Weinreb (1998), Liu, Kripke, Twa, Gokhale, Jones, Park, Meehan and Weinreb (2002) and Liu, Bouligny, Kripke and Weinreb (2003b) found in young, emmetropic, adults a tension trough in the evening (9.30pm) and a peak at the last sleep measurement (5.30am). While posture was found to influence the magnitude of IOP, it did not change the timing of peaks and troughs. Liu, Kripke, Hoffman, Twa, Loving, Rex, Lee, Mansberger and Weinreb (1999a) also found that light did not affect the sleep-induced peak for young healthy adults with the peak again noted at 5.30am just at the end of the sleep period.

Young moderate myopes, with normal wake/sleep posture, upright while awake and supine at night, showed a similar IOP pattern to that illustrated with young emmetropes; a trough at 9.30pm and a peak at 5.30am (Liu *et al* 2002). Posture however was shown to have an over-riding effect on this sample group. When the subjects remained supine throughout the 24-hour period a trough was noted at 1.30am, well within the sleep period, and a peak between 11.30am and 1.30pm. The authors also suggest that the more severe the myopia, the less IOP will elevate at night.

Age was demonstrated to change the sleep/wake tension cycle (Liu, Kripke, Twa, Hoffman, Mansberger, Rex, Girkin & Weinreb 1999b). A trough was still recorded at 9.30pm, at the end of the 'Awake' period, but the peak was found earlier in the sleep period at 11.30pm. As in the Liu *et al* (1998 & 2003b) papers posture was shown to affect the magnitude of tensions recorded but did not affect the timing of troughs and peaks.

While most recent research seems to support the concept of sleep induced IOP peaks in healthy subjects (Frampton *et al* 1987, Brown, Morris, Muller, Brady & Swann 1988a, Brown *et al* 1988b, Wildsoet *et al* 1990, Birchley *et al* 1990,

Buguet *et al* 1994, Liu *et al* 1998) and ageing eyes (Buguet *et al* 1994, Liu *et al* 1999b), there is some conflict as regards glaucomatous eyes.

Ido *et al* (1991) investigated the circadian rhythm of normal-tension glaucoma patients. Using a Goldmann, but in close proximity to the subjects and able to record tensions within 3 to 10 minutes of arousal, these authors did not find any sleep induced pressure peaks and concluded that sleep had little or no effect on 'diurnal' (term used in this paper) variations. The subjects in this study had a mean age of 58.2 (range 32 to 86) and all were normal tension glaucoma suspects. The authors suggest that the age difference in their sample group could explain the difference in results with the Frampton and associate's study, which had a much younger group. Wilensky (1991) however, using subjects ranging in age from 31 to 79, found sleep related IOP peaks for both normal and glaucomatous eyes, regardless of age.

Orzalesi, Rossetti, Invernizzi, Bottoli and Autelitino (2000), found pressure troughs at 3.00am and peaks at 9.00am for untreated and treated glaucoma patients. These authors woke the subjects 10 minutes before recording IOP and blood pressure. While this delay in recording has been shown to mask any IOP spikes (Frampton *et al* 1987, Brown *et al* 1988b) Orzalesi and co-workers used identical recording techniques on a control group of young, non-glaucomatous eyes and detected IOP peaks during sleep. Noel, Kabo, Romanet, Montmayeur and Buguet (2001), comparing healthy and glaucomatous Africans, also noted this reversal of the peak IOP values for glaucomatous subjects versus non-glaucomatous volunteers. Healthy volunteers had highest IOP values during 'Slow Wave' sleep while the glaucoma patients had peaks while awake during the afternoon.

Liu, Zhang, Kripke and Weinreb (2003a) found that with habitual body posture, upright while awake and recumbent at night, IOP peaks were found in both the untreated glaucoma and control groups during sleep. Wilensky (1991), Wildsoet *et al* (1993) and Zeimer *et al* (1990) also presented data supporting the sleep related rise in IOP for both normal and glaucomatous eyes.

Martin (1987) remarks with interest that Schiotz in 1908, Adler in 1950 and Duke-Elder in 1952 proposed that IOP increases during the night to reach a maximum in the early hours, prior to waking. The body of literature over the last 18 years seems to support this concept of IOP peaks during sleep. These peaks appear to be independent of a circadian rhythm, but influenced by a number of physiological variables.

In this current research IOP was measured over a 24-hour period, with a variety of sleep times to assess whether sleep induced peaks were evident.

Prostaglandin Analogues : Efficacy and Instillation Modalities.

Prostaglandin analogues are becoming the mainstay of medical treatment for the majority of glaucomas (Heath 2002, Heath 2004).

Phelan (2002) states that - 'a major advantage of Latanoprost over previous medical treatments for glaucoma is that it is effective with only a single dose, preferably in the evening.' No reason for the preference for evening instillation is given.

Heath (2002) suggests that evening instillation is more effective in lowering IOP than morning administration, this assertion being based on a single reference, that of Alm and Stjernschantz (1995). A letter from Pfizer Global Pharmaceuticals (Appendix 2) states that latanoprost is only licensed for administration at night and also cites the Alm and Stjernschantz paper, but no others, as support for that clinical decision. While not stated, the absence of any other references supporting evening administration in this letter does infer that this paper must have been pivotal in the decision to license prostaglandin analogues specifically for evening use. Alm and Stjernschantz did report that evening administration was more efficacious in lowering IOP than morning dosing, but went on to report that pressure was recorded 12, 16 and 20 hours after evening application but 4, 8 and 24 hours after morning applications. They

remark that maximal drug effect is after 12 hours, which would necessarily bias their results toward favouring the evening dosage.

Gelatt and MacKay (2001) experimenting on beagles suggested that both morning and evening administration produced excellent IOP reduction. The results for morning instillation showed a slight spike about 8.00am so the authors favoured evening dosage as allowing less daily fluctuation.

Camras (1996a) favoured evening administration to block any potential early morning IOP spikes. The author does not support or give any reference as to why he would suspect such a spike.

A study by Watson (1998) found no difference in the efficacy of morning or evening administration of latanoprost. This was a longitudinal study with the results based on a 24-month patient trial.

Kontas *et al* (1999), comparing morning (8.00am) and evening (10.00pm) dosing of Latanoprost, found their results equivocal. The conclusion made was that evening instillation gave a lower reading at about 10.00am while morning administration gave better results at 10.00pm. These authors also remark that the study by Alm and Stjernschantz (1995) only demonstrated an increased efficacy of evening over morning administration in reducing IOP during daytime hours. Kontas and associates suggest that it is premature to assume either morning or evening dosing to be superior in controlling IOP over a nyctohemeral period. Significantly they concluded by suggesting that the timing of a patient's personal IOP peak, if it could be ascertained, could be an important factor in timing drug administration.

Kontas, Nakos, Tersis, Lallos, Leech and Stewart (2002), compared a morning/evening dosing of a latanoprost/timolol combination. While the potential for the timolol to mask a pure prostaglandin hypotensive effect, this study again supported the earlier Greek research which suggested that morning

administration gave better IOP reduction in the afternoon while evening medication produced maximal results the following morning.

Racz *et al* (1996) presented data suggesting that morning instillation gave excellent circadian reduction in IOP. While IOP reduction is shown to be equal across the nyctohemeral period when comparing the treated to control (untreated) eyes, the graphs do still suggest that there are nocturnal peaks for both treated and controls. Bito, Racz, Ruzsony, Nagy, Gagyi and Carino (1994) also chose morning administration of latanoprost and also confirmed excellent hypotensive effects. Kiuchi, Takamatsu and Mishima (1994), comparing 7.00am and 7.00pm administration of latanoprost, could find no clear-cut difference in efficacy between the two administration times.

A number of papers, comparing various drug concentrations or types, seem to arbitrarily stipulate morning or evening instillation. No rationales are given, but in every case the timing of instillation allowed measurements to be taken within working hours; suggesting the choice of instillation was made for logistical, rather than clinical reasons. Alm and Villumsen (1991), Villumsen and Alm (1992) and Hotehama, Mishima, Kitazawa and Masuda (1993) chose morning instillation, while Nagasubramanian, Sheth, Hitchings and Stjernschantz (1993), Watson and Stjernschantz (1996), Saito, Takano and Shirato (2001) and Linden and Alm (2001) preferred evening instillation.

While the literature does not support irrefutably the popular use of evening prostaglandin instillation as the most effective in reducing IOP, there does seem to be more agreement on the drug response time. The literature suggests that the maximal drug effect appears to be between 8 and 12 hours after administration (Alm & Villumsen 1991, Hotehama & Mishima 1993, Hotehama *et al* 1993, Villumsen & Alm 1992, Product Monograph – Pfizer Canada 2004). Kontas *et al* (1999) however do give a more guarded estimate of response times; suggesting that, while the exact timing is unknown, it is probably about 8 hours.

Kontas *et al* (1999) used 10.00pm as their evening slot, Kiuchi *et al* (1994) used 7.00pm, other investigators chose 8.00pm for evening instillation (Gelatt & MacKay 2001, Konyas *et al* 2002, Camras 1996, Watson & Stjernschantz 1996, Nagasubramanian *et al* 1993, Hotehama & Mishima 1993), Saito *et al* (2001) designated 9.00pm, Alm and Stjernschantz (1995) and Watson (1998) did not designate a time more specifically than in the evening, while the latanoprost licence simply specifies administration at night. The timing of instillation could be significant if sleep induced peaks exist to ensure the most effective drug response coincides with the pressure peak. Giving patients a more specific time to instil medications other than simply before bed, which presumably could be interpreted as anywhere from early to late evening, may be clinically important.

Prostaglandins are pro inflammatory chemical mediators (Camras 1996b) and as such can cause some degree of conjunctival hyperaemia. Alm and Stjernschantz (1995), Alm, Villumsen, Toernquist, Mandahl, Airaksinen, Tuulonen, Marsk, Resul and Stjernschantz (1993), Hotehama and Mishima (1993), Hotehama *et al* (1993), Nagasubramanian *et al* (1993) and Watson and Stjernschantz (1996), all comment that the hyperaemia noted peaked between 4 and 8 hours after instillation. At therapeutic doses the hyperaemia was described in all the studies as very slight or mild however prostaglandins did produce statistically more hyperaemia than beta-blockers. A clinical decision to administer prostaglandins in the evening may be as much to ensure hyperaemia occurs during sleep than because of any perceived improvement in efficacy of evening dosing (confirmed by Mr Michael Birch FRCS FRCOphth, consultant ophthalmologist RVI – personal communication).

This experiment was conducted to try to establish the existence of a sleep induced IOP rise in normal individuals. If predictable IOP peaks exist, and since the maximal effect time for these drugs is known, then we may be able to recommend a more appropriate drug administration modality to give enhanced ocular hypotensive results.

SUBJECTS AND METHODS

Tensions were recorded over a continuous 24-hour period.
All subjects were volunteers and were either members or leaders of the 'First Ashington Scout Group'.

Consent and Ethics Approval.

Informed consent was obtained from all subjects.

Since a proportion of the subjects were minors, an open parent meeting was organised at a local school. During this meeting the experimental goals were explained to both subjects and parents. The voluntary nature stressed and questions answered. An information leaflet was distributed for guardians and subjects with a consent form attached (Appendix 3).

All subjects showing an interest were booked in for full eye examinations at the optometry practice. Signed consent forms were collected after the eye examination.

Northumberland Local Research Ethics Committee was approached for ethics approval. This was given contingent on confirming indemnity cover (Appendix 4). This was not forthcoming since the experimental procedures were not carried out within the practice. The cost of indemnity cover for off practice procedures, not construed as domiciliary testing, was restrictive and unaffordable. Consequently, while informed consent was obtained ethics approval was not.

Pulsair 3000.

Intraocular pressure was recorded hourly, while the subjects were awake and every two hours once asleep, using a calibrated Keeler Pulsair 3000. Fisher, Watson and Spaeth (1988) demonstrated the importance of regular calibration in

maintaining accuracy. The tonometer was two weeks old prior to commencement and was calibrated, arriving in time to do the pre-assessment.

As with other non-contact tonometers, the Pulsair 3000 gives a rapid measurement, requires no anaesthetic and can be used repeatedly without causing corneal damage (Augsburger & Alexander 1982). Shields (1980), Vernon (1989) and Pointer (1999) also comment that NCT recordings are objective and suggest reduced cross contamination risks. Further, the Keeler Pulsair can be used with the subject in any position allowing them to remain supine during the sleep periods. The more compact design of the Pulsair 3000 over earlier pulsairs allowed it to be carried with one hand, making it extremely convenient in this particular experimental setting.

The tensions were recorded in the right eye only, except for one subject who had an epithelial basement membrane disorder in this eye so the left was designated. A single eye per subject was used to make data collection faster and less disruptive to sleep patterns. Since normal individuals demonstrate little between eye asymmetry no extra information would be expected by testing both eyes (Carel, Korczyn, Rock & Goya 1984, Leydhecker 1976, Pointer 1997).

Introduced in 1998 the Pulsair 3000 represents the most refined and presumably the most accurate portable non-contact tonometer currently available. Parker, Herrtage and Sarkies (2001) show a good correlation with Goldmann and found a standard deviation from Goldmann of only 1.1179mmHg. Using the Bland and Altman (1986) analysis techniques, 95% of readings fell within ± 2.24mmHg of the mean difference between Goldmann and Pulsair 3000 measurements and bias from the mean difference was only –0.48mmHg. Grolman, Myers and Lalle (1990) state that the ISO criterion for standard deviation for certification and verification of tonometers is 2.5mmHg. These authors also state that the standard deviation of one Goldmann operator to another can be in the order of 3.0mmHg so the Parker and associate's results confirm the suitability of the Pulsair 3000. Using a different approach, but also confirming the Pulsair's suitability, Vernon, Jones and Henry (1991) found that taking four pulses per

eye with the Pulsair 2000 ensured a sensitivity of referral of 91.7% and a specificity of referral of 95.6% when compared to the ophthalmology department's use of Goldmann.

To keep measurement time and patient disruption to a minimum while trying to maximise accuracy this study accepted the average of the first five consecutive readings as suggested by Moseley, Evans and Fielder (1989). A fuller discussion of the rationale for this decision is given in Appendix 5.

Non-contact tonometers have been shown by some authors to show good correlation with Goldmann only if the tensions are below 35mmHg and the corneas are normal (Sorenson 1975, Shields 1980). Fisher *et al* (1988) did not suggest an increase in the standard deviation at pressures up to 50mmHg for the Pulsair 2000 and Bonomi, Baravelli, Cobbe and Tomazzoli (1991) found reproducibility of the Pulsair was good for pressures over 24mmHg although they did suggest it was better for tensions below this figure. All subjects in these experiments were normotensive during awake periods and no tension exceeded 28mmHg during sleep.

Sleep Depth.

No access to polysomnography was available, but some level of sleep depth quantification was deemed necessary. Rechtschaffen and Kales (1968) classify sleep into five categories plus a sixth for wakefulness, Stage W = wakefulness, stages 1 to 4 and REM sleep. Without polygraphic traces accurate differentiation of all five sleep stages was impossible. However, a modification of the grading system used by Buguet *et al* (1994) was adopted. These researchers, using electro-physiological devices, considered only (1) Wakefulness, (2) Light Sleep (Stages 1 and 2), (3) Slow Wave Sleep (Stages 3 and 4) and (4) REM Sleep (rapid eye movement). We used these categories with the exception that we could not differentiate Slow Wave Sleep from REM sleep. A subjective assessment of sleep level was made by the assistant and recorded independently of the tonometer operator.

Grades used were :

1. Wakefulness : patient responded to our approach unsolicited, either by talking or opening their eyes as we knelt beside them.
2. Light Sleep : only very slight effort required to rouse subject. Light touch to shoulder or gentle shaking. Response time to opening eyes and acknowledging our presence less than 10 seconds.
3. Deep Sleep : including Slow Wave Sleep and REM sleep. Vigorous waking required, delay with subject confusion evident on waking, possibly with recovery of Bells phenomenon noted.

The tonometrist took the required readings blind to the sleep depth grade assigned to the individual. If a subject was given different grades at different sample points during a sleep period the final overall grade assigned for that subject for data analysis was the one representing deepest sleep level.

Pre-Assessment and Exclusion Criteria.

Prior to the data collection every candidate underwent a full eye examination at the practice.

A thorough ocular history excluded any family or personal history of glaucoma, as well as any symptoms of sub-acute angle closure and corneal or other pathologies. General health issues were also investigated; smoking, systolic blood pressure, heart rate and diabetes have all been shown to have some level of correlation with IOP (Carel *et al* 1984). A proportion of the study group did smoke but no other health issues were reported. No one requiring chronic use of medications was included, primarily because of the isolated data collection site. Fundoscopy showed all discs to be normal with healthy neural rims. Tensions at this daytime examination were all below 20mmHg.

Because of the age of some of the volunteers and the subjective nature of the test, fields were only checked for the adults or if tensions and disc appearances

were equivocal. In the case of the scouts, field assessments were never felt necessary. The adult candidates had normal fields confirmed on the Medmont Perimeter using the 'Glaucoma Fast Threshold' strategy. False positive, false negative and fixation loss confirmed each candidate's reliability. The programme did not flag any of the global indices of Overall Defect (OD), Pattern Defect (PD), Short-term Fluctuation (SF) and Cluster Analysis (CA) as statistically significant for the volunteers included in the research.

Slit lamp biomicroscopy, Eyesis corneal topography and keratometry confirmed healthy corneas, anterior chambers and irides. Angle depth was estimated using the van Herrick technique in preference to zeiss gonioscopy. While van Herricks cannot substitute for gonioscopy (Palmberg 1996) it was considered appropriate in this instance because of the number of young subjects. Further, no other signs of glaucoma were detected and under normal clinical conditions gonioscopy would not have been considered necessary. The van Herrick method grades angle depth from grade I (peripheral angle depth less than one fourth corneal thickness) to grade IV (angle depth equal or greater to the corneal thickness). Patients with angles graded I or II were excluded as Palmberg remarks that angles up to and including grade II have been found on gonioscopic examination to be closed.

One eye was excluded from the study due to reported recurrent epithelial erosions caused by an epithelial basement membrane disorder. This was considered prudent since very extensive repeated measurements have been shown to cause minor epithelial defects in some cases (Shields 1980). No other exclusion anomalies were detected.

Apart from confirming ocular normality the eye examination allowed the tonometer to be demonstrated and handled by the subject. In the case of all scout members a parent or guardian was present throughout the examination. Before the consent forms were collected every patient and guardian was invited to ask further questions, perhaps not addressed at the parent evening.

No alcohol was allowed during the experimental period as this has been shown to decrease IOP (Shields 1982). Strenuous exercise has also been implicated in causing reduced IOP (Shapiro, Shoenfeld & Shapiro 1978). Strenuous exercise was difficult to discourage, but all subjects relaxed for 15 minutes prior to readings.

The Experiment.

Twenty-five members and leaders of 'First Ashington Scout Group' were enrolled. The mean age was 21 with a range from 10 to 53. A scout camp was organised specifically for the data collection over a Saturday/Sunday during March 2003. The official 'Scout' campsite, consisted of a main hut with cooking, toilet, recreational facilities as well as some sleeping accommodation. Four large tents were erected within 10 metres of the main hut for extra sleeping arrangements.

No specified sleep period was designated; all subjects retired at their own choosing. Since a sleep induced peak was postulated, it did not matter when the sleep period occurred and a deeper sleep was predicted if the subject went to bed voluntarily. Sleeping positions were arranged so that the observer could walk between subjects, wake them momentarily to record pressure, while leaving the subject in bed and supine.

During the day a variety of activities were organised by the leaders, with the volunteers returning to the main hut every hour for pressures to be recorded. In the evening board games and television were supplied. During sleep periods the tonometer was attached to a 20m electric flex allowing the investigator to reach every sleeping spot without alerting the subject. Lights were not used and the readings quietly read to an assistant for recording.

Due to the logistics of organising the campsite measurements were not commenced until 5.00pm.

RESULTS

Most other research in this area stipulates uniform sleep periods, allowing composite curves of all results to be generated. Because of the totally individual sleep times encouraged in this experiment and the relatively small number of subjects, every individual's nyctohemeral curves are included.
Measurements taken while subjects were awake are represented as open diamonds. Measurements during episodes of 'light' sleep are red circles. Black squares represent IOP taken when the subject's sleep level was graded as 'deep'.

Standard Deviation and Error Bars

The nature of the data collection did not allow Standard Deviations (SD) to be calculated. Each single tension plotted is the average of five instantaneous pressures taken within the ocular pulse cycle. Even if all five instantaneous readings were recorded separately, which could have significantly disrupted sleep, the SD thus calculated would represent the variability of instantaneous readings within the pulse cycle. No information would be gained regarding the SD of the published intraocular pressure recording technique.

A gauge of measurement error was calculated separately using the same calibrated Pulsair 3000 in the practice. A range of volunteers had five cycles of five instantaneous readings each, allowing the calculation of the standard error of the measurement technique. A conservative estimate of error for the machine method of obtaining a single IOP reading was 1.5mmHg.

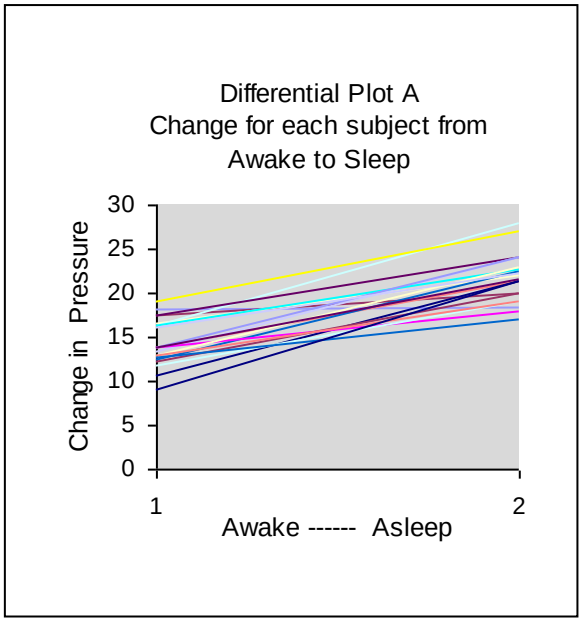
Statistical Techniques

The hypothesis tested is that the mean, 'Asleep' IOP is higher than the mean 'Awake' pressure.
No statistical analysis was done for the subjects remaining awake.

Visual inspection of subjects who only achieved sleep levels graded as ‘light’ do not suggest significant changes in IOP during these sleep episodes. Regardless, all sleep measurements recorded for both ‘deep’ and ‘light’ sleep grades were used in the analysis. This gives a more conservative estimate of significance and eliminates the possibility of the grader having misjudged the level of sleep.

Since the sample size was less than 30, paired t-distribution was used to test for an absolute difference between ‘Awake’ and ‘Asleep’ IOP.

The mean change in IOP from ‘Awake’ to ‘Asleep’ was plotted. The rise in IOP as the subject passes into sleep is clearly evident. Visual inspection suggests two general slope gradients, appearing to equate to ‘light’ sleep subjects versus ‘deep’ sleep subjects.



IOP during sleep was found to be significantly higher than IOP while awake. The difference between mean ‘Awake’ IOP and mean ‘Asleep’ IOP was found to be 7.387mmHg. 95% confidence range for this figure was from 5.991 and 8.782mmHg (The raw statistical data is presented in Appendix 6).
Inclusion of every nyctohemeral plot for visual comparison was considered appropriate.

<u>Sleep Depth 1 - Awake</u>

Figures 1 to 3 are the nyctohemeral curves for volunteers who did not sleep at all during the data collection period. Subject 1 (Fig 1) was upright throughout, while subjects 2 and 3 did attempt to sleep, so were supine during rest periods. Apart from short-term IOP fluctuations no trends are obvious from these

nyctohemeral plots. No statistical analysis was necessary; error bars clearly show no separation of IOP.

Figure 1 : Subject 1 (Age 40) - Sleep Grade 1

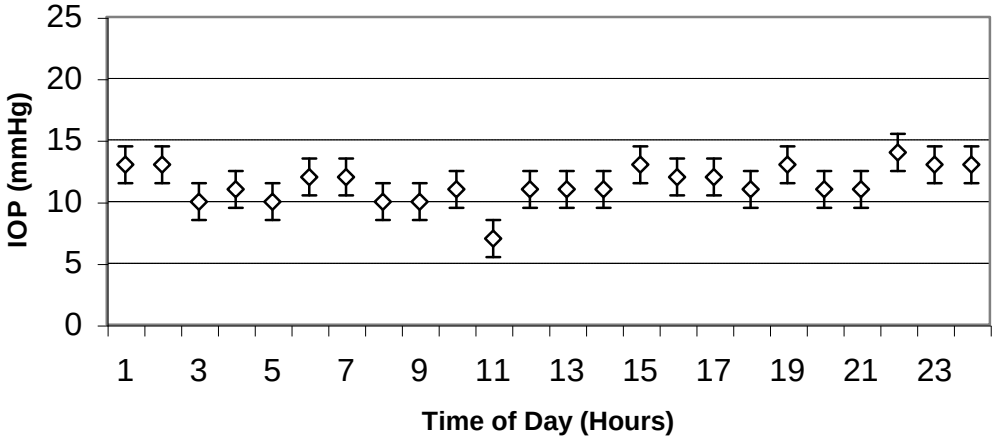


Figure 2 : Subject 2 (Age 53) - Sleep Grade 1

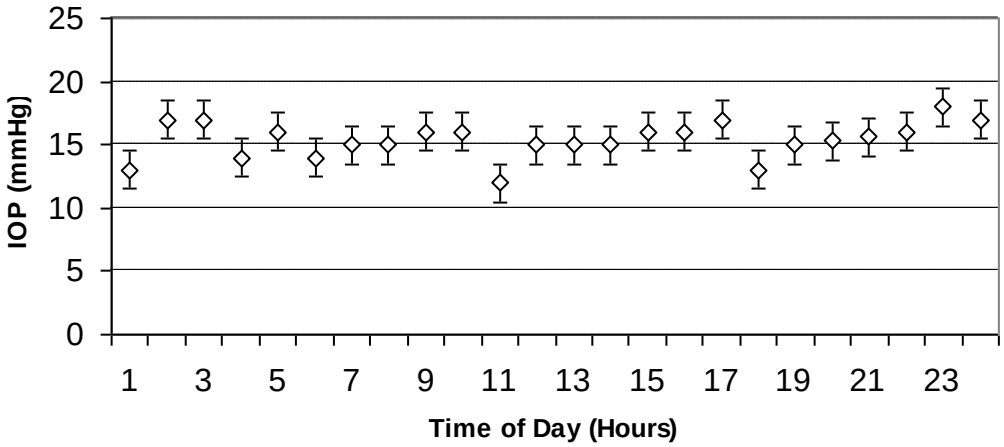
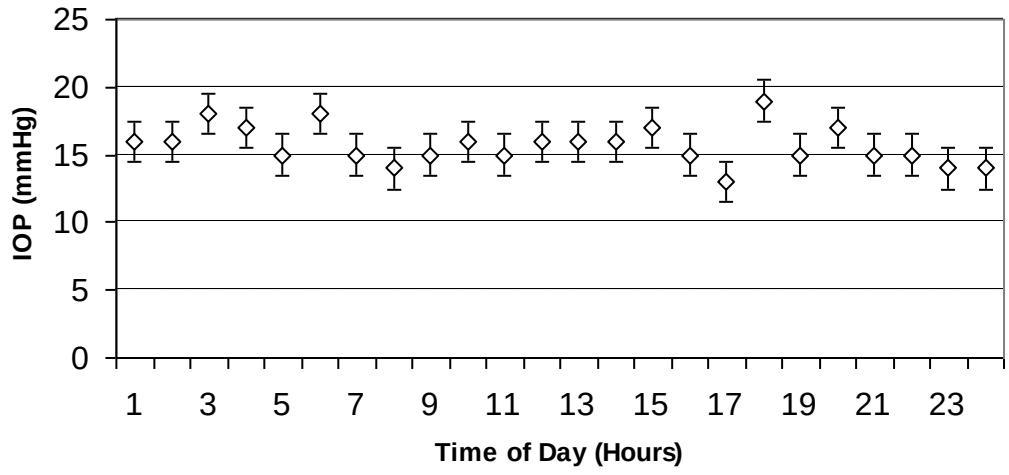


Figure 3 : Subject 3 (Age 19) - Sleep Grade 1



Sleep Depth 2 – Light Sleep

Figures 4 to 7 are the nyctohemeral curves for subjects with sleep graded as 2, 'light'.

Error bars do not suggest a clear distinction between 'Asleep' levels of IOP and 'Awake' levels. No statistical analysis on these four subjects, specifically, was conducted; the data was collated with 'deep' sleep subjects for statistical analysis.

Figure 4 : Subject 4 (Age 39) - Sleep Grade 2

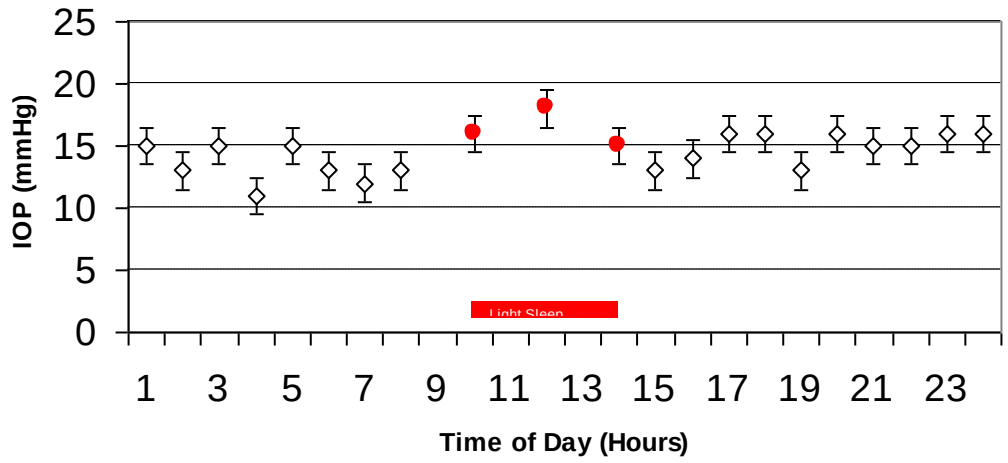


Figure 5 : Subject 5 (Age 13) - Sleep Grade 2

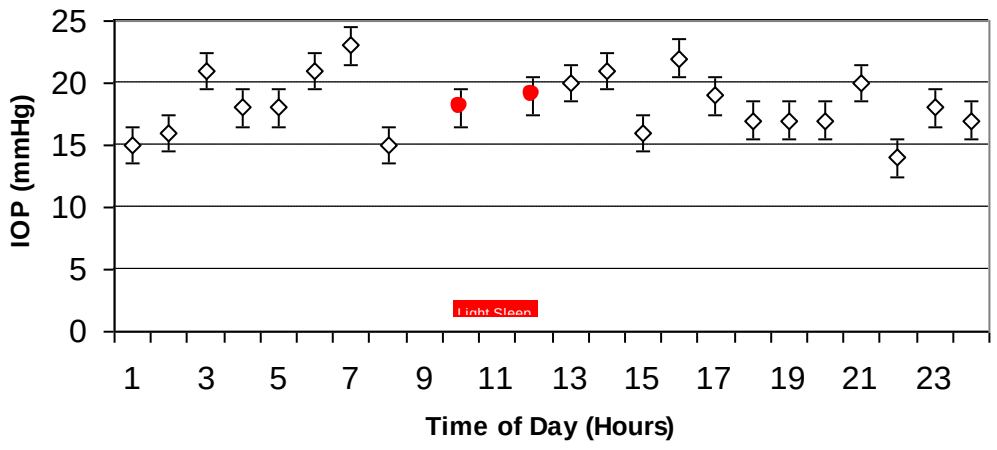


Figure 6 : Subject 6 (Age 18) - Sleep Grade 2

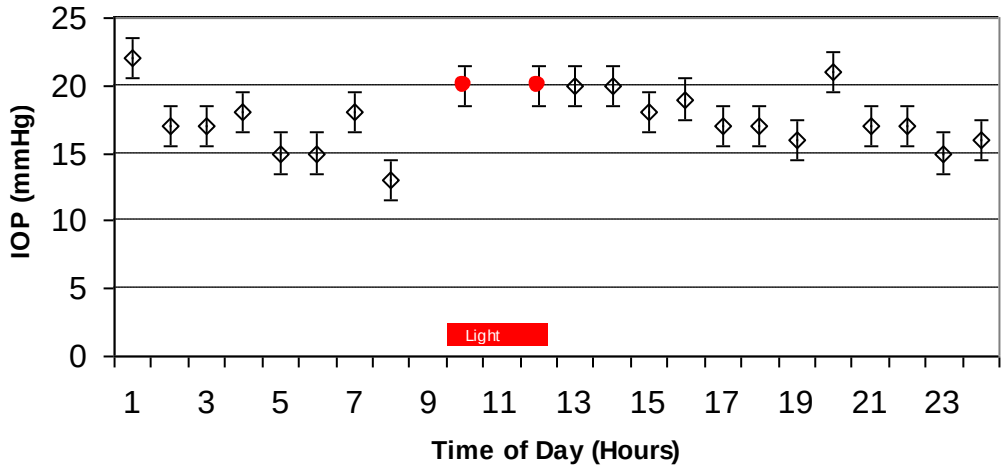
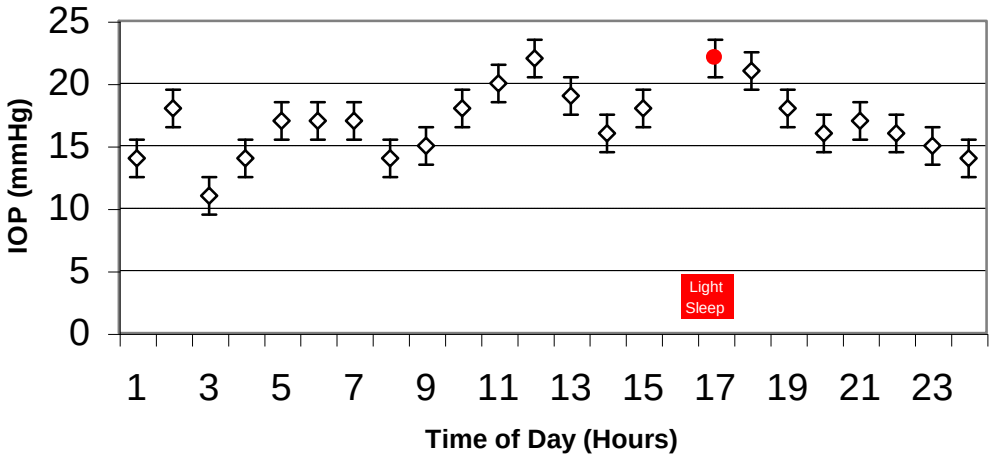


Figure 7 : Subject 7 (Age 53) - Sleep Grade 2



Sleep Depth 3 – Deep Sleep

Dramatic rises in IOP become evident when the subjects sleep level is graded as 'deep'. Of the 18 volunteers who slept soundly only two, subjects 14 and 23 (Figs 14 & 23) do not have clear separation, as evidenced by the error bars, of the 'Awake' pressures and 'Asleep' pressures.

Further, the IOP elevations were independent of sleep duration or time of day. Subject 8 (Fig 8) for instance, had only a single pressure reading while asleep – collected during a sleep period of only about two hours. The sleep episode was mid afternoon.

Figure 8 : Subject 8 (Age 15) - Sleep Grade 3

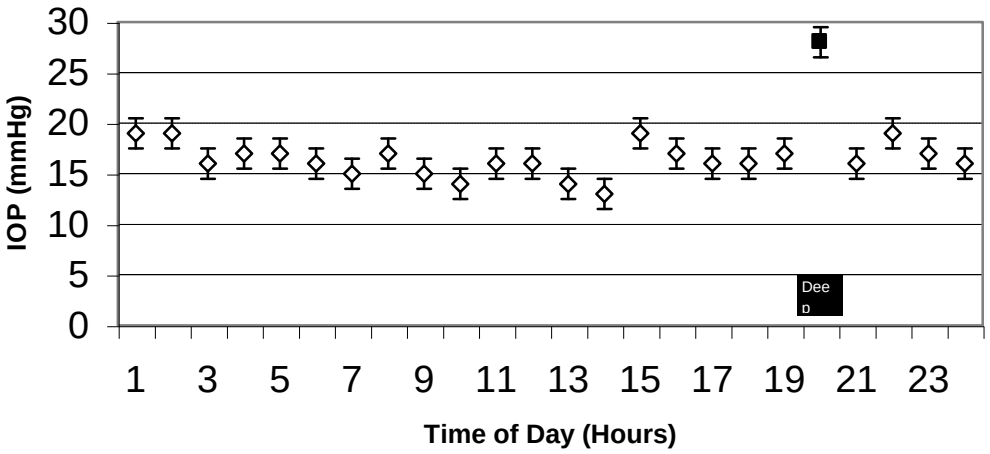


Figure 9 : Subject 9 (Age 11) - Sleep Depth 3

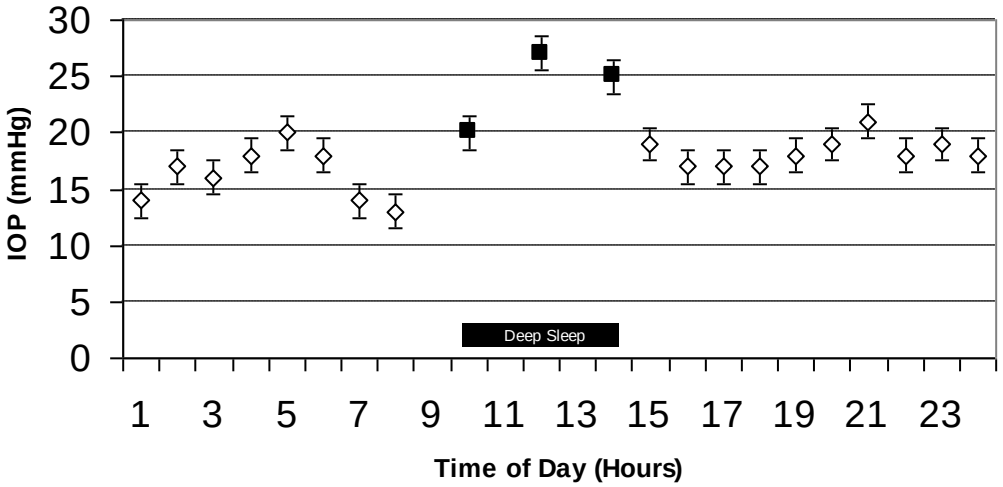


Figure 10 : Subject 10 (Age 10) - Sleep Depth 3

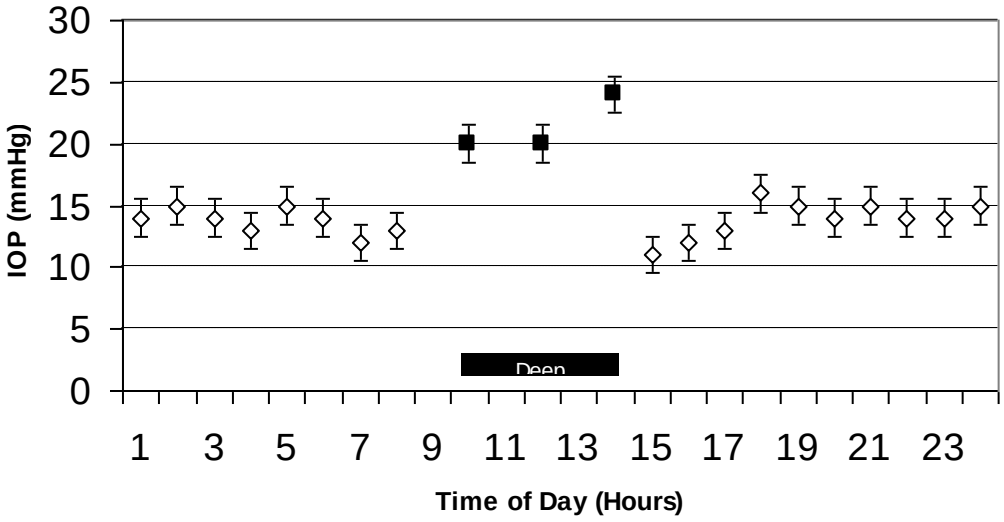


Figure 11 : Subject 11 (Age 10) - Sleep Depth 3

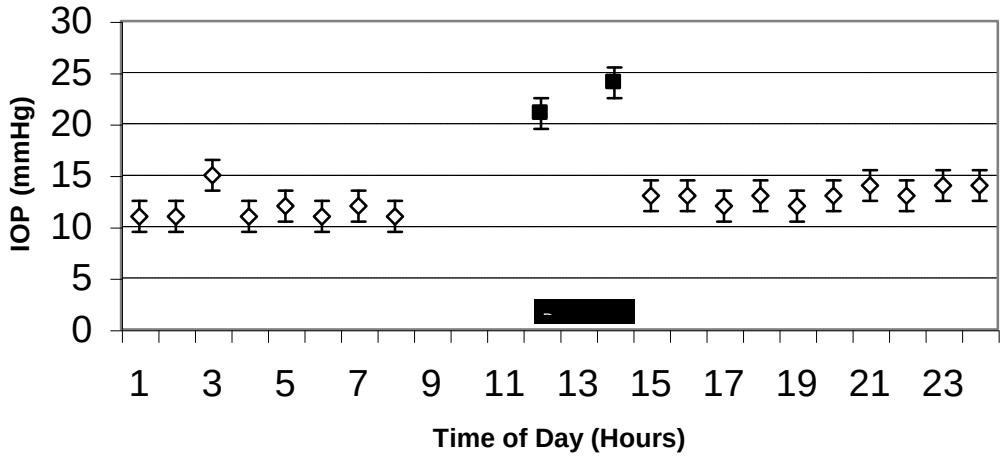


Figure 12 : Subject 12 (Age 11) - Sleep Depth 3

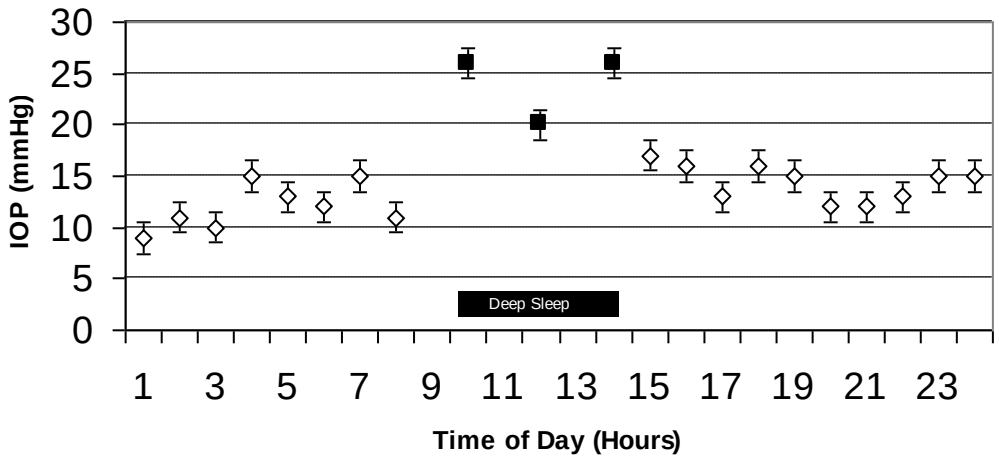


Figure 13 : Subject 13 (Age 37) - Sleep Depth 3

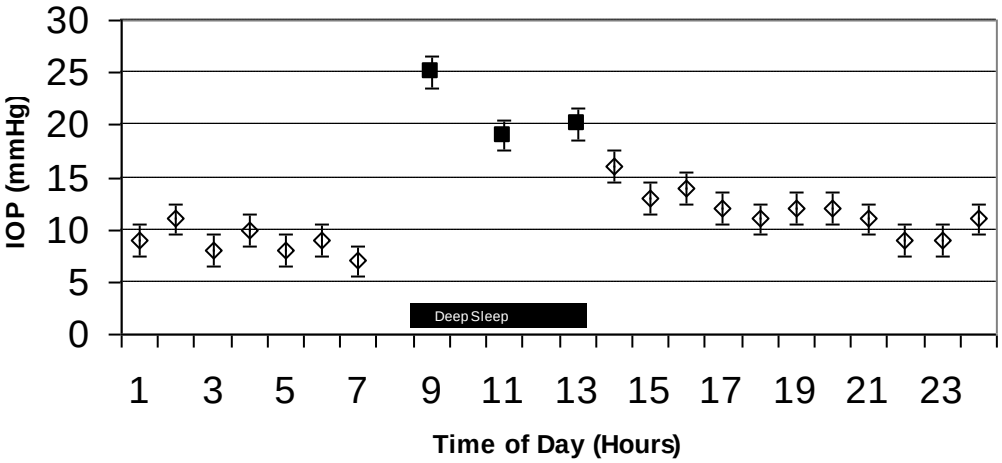


Figure 14 : Subject 14 (Age 15) - Sleep Grade 3

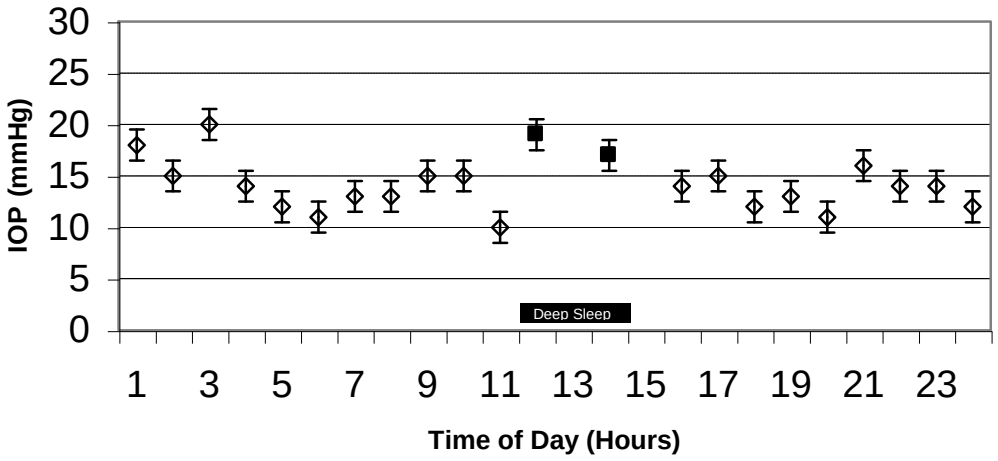


Figure 15 : Subject 15 (Age 24) - Sleep Grade 3

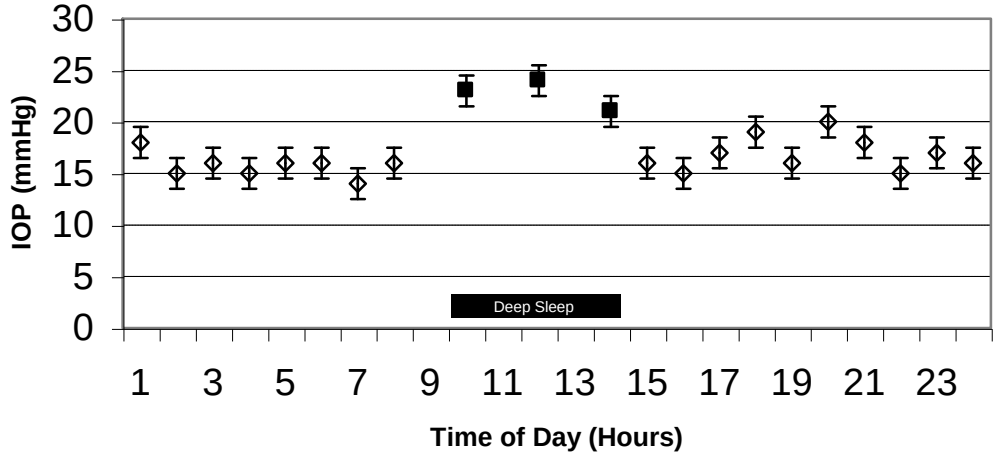


Figure 16: subject 16 (age 26), sleep depth 3

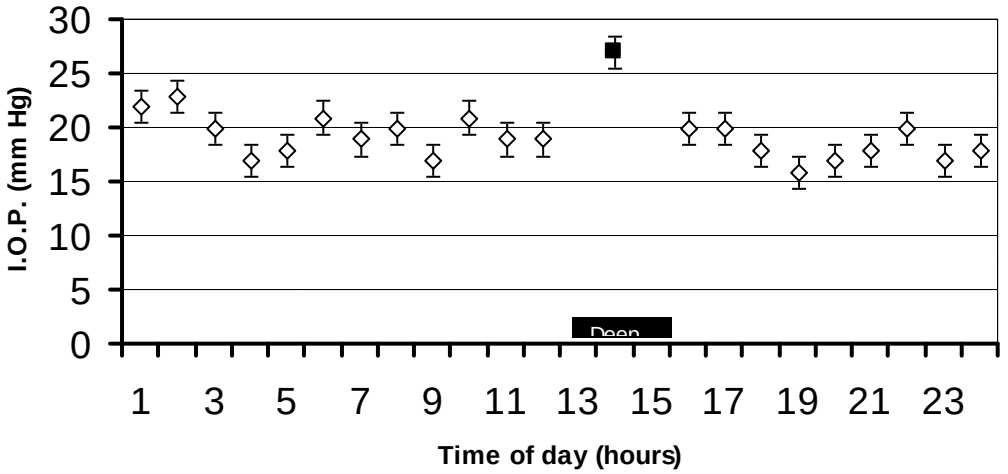


Figure 17 : Subject 17 (Age 13) - Sleep Grade 3

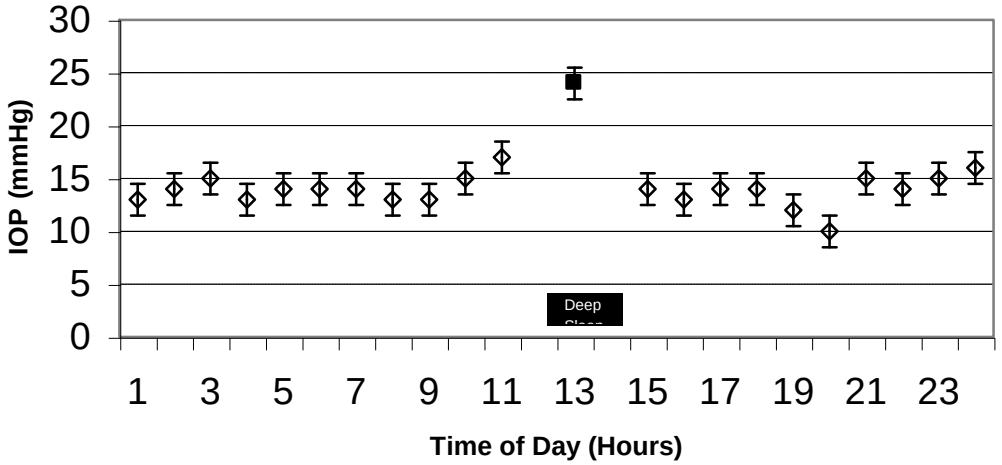


Figure 18 : Subject 18 (Age 13) - Sleep depth 3

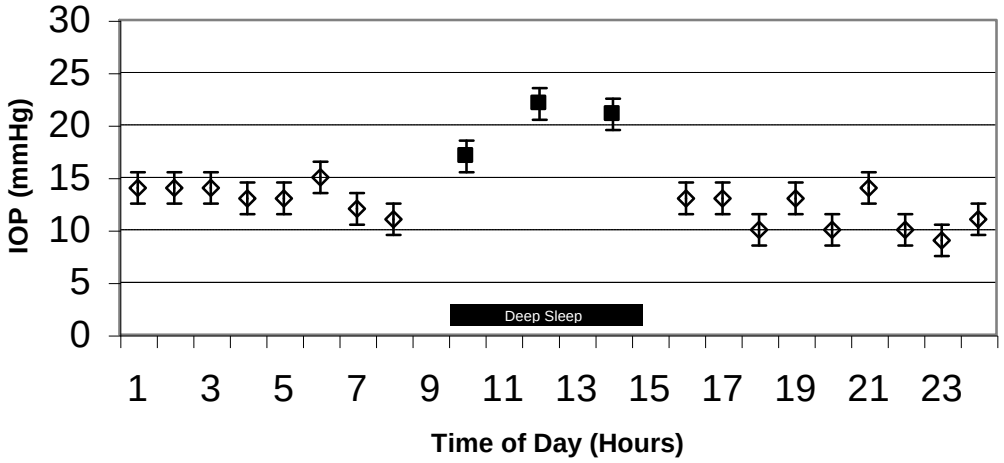


Figure 19 : Subject 19 (Age 16) - Sleep Depth 3

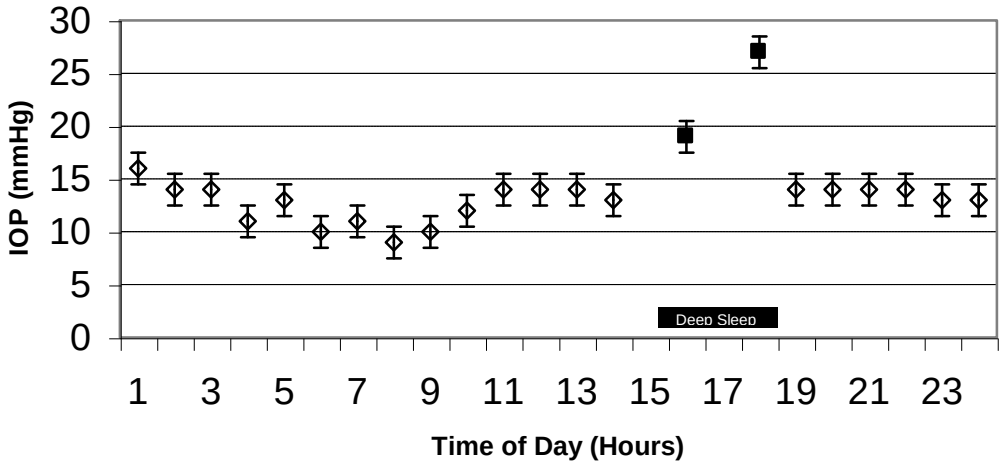


Figure 20 : Subject 20 (Age 14) - Sleep Depth 3

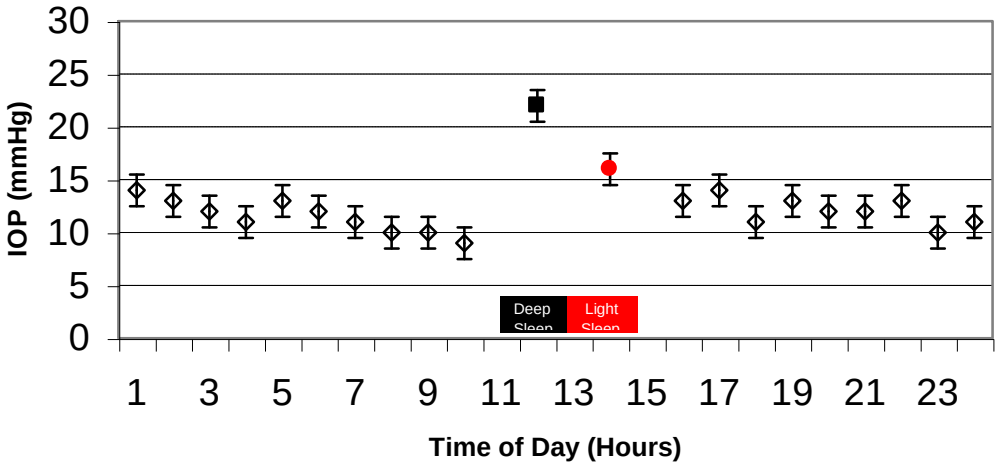


Figure 21 : Subject 21 (Age 15) - Sleep Depth 3

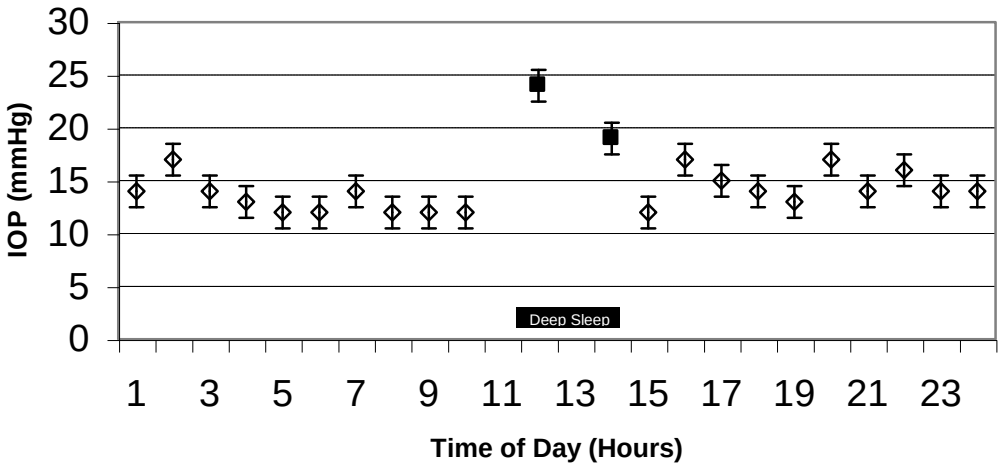


Figure 22 : Subject 22 (Age 13) - Sleep Depth 3

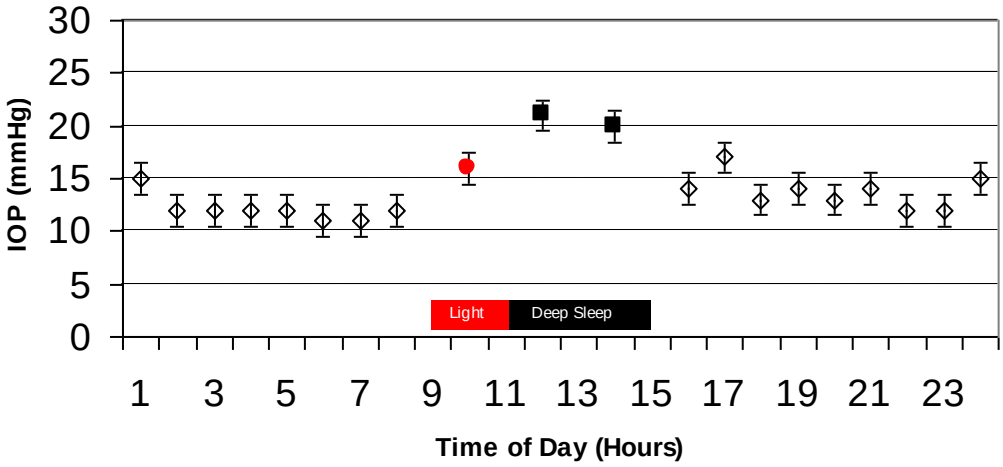


Figure 23 : Subject 23 (Age 35) - Sleep Depth 3

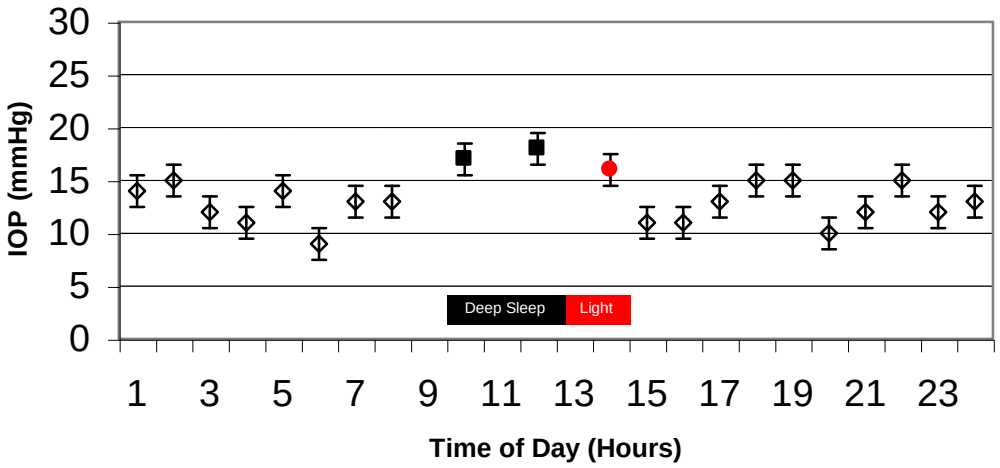


Figure 24 : Subject 24 (Age 10) - Sleep Depth 3

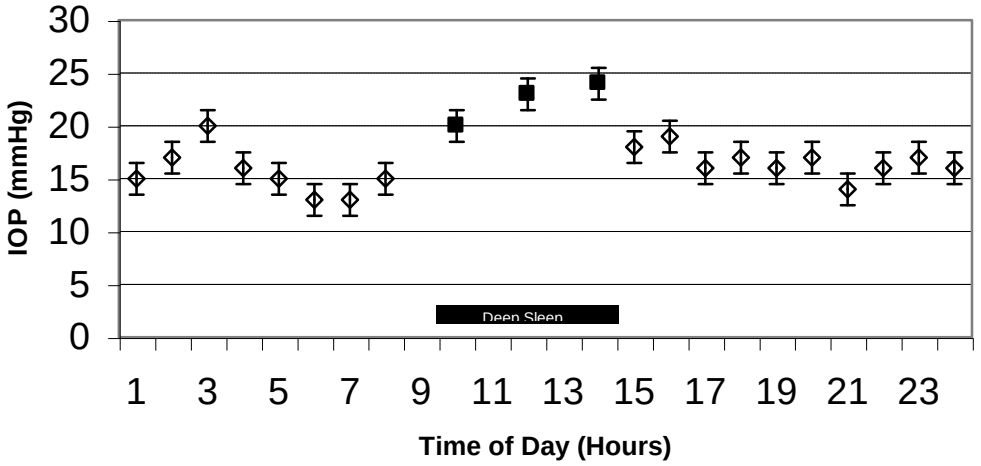
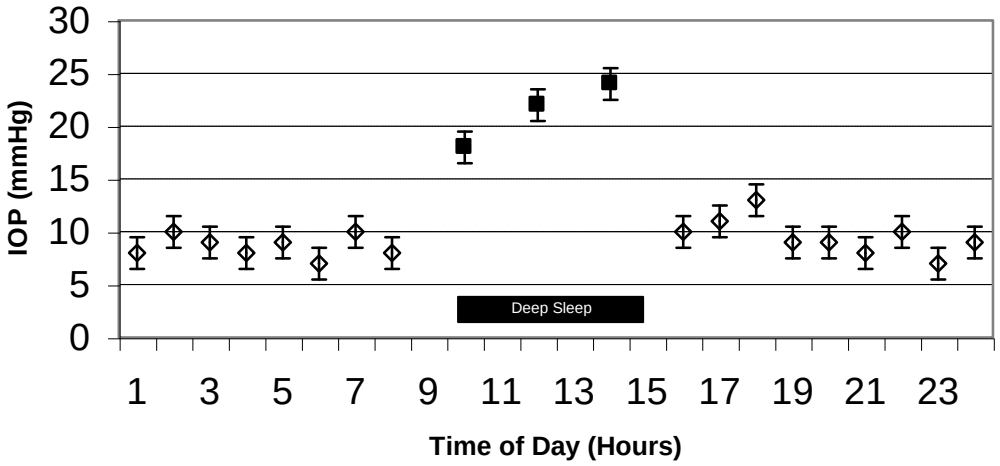


Figure 25 : Subject 25 (Age 11) - Sleep Depth 3



METHODOLOGY AND INSTRUMENTATION CRITIQUE

Wilensky (1991), in a very broad study, considered a number of parameters that could affect IOP. Each variable was considered and discussed in isolation. The 'Diurnal IOP Study', suggested that 'daytime' curves, IOP highest between 8.00am and 2.00pm, were most prevalent. When specifically addressing the influence of sleep on IOP, sleep induced pressure peaks were observed in both normal and glaucomatous eyes. This single paper could be cited to support either daytime or sleep associated IOP peaks.

The enormous array of conflicting information in the literature undoubtedly mirrors the differences in study designs, instrumentation, subject profiles and sample sizes.

Authors tend to reference papers that lend support for their instrumentation or methodology. In this way errors and misinterpretations can be propagated throughout related research. Many researchers have ingenuous intentions to build on previous work, maximising results without duplication. Smith (1985), attempting to correlate progression of glaucomatous field loss to specific attributes of a circadian tension profile, did not sample nocturnal pressures. This was because all current literature of that time indicated that pressure troughs are present at night and therefore sampling this period was superfluous. Zeimer *et al* (1991), also trying to ascertain which aspect of a pressure profile is more damaging only sampled five times during the nyctohemeral period. Ensuring one measurement was done as the subject woke, specifically sampled an area these authors felt was significant based on a previous paper by Zeimer *et al* (1990).

This potential problem is so crucial to the discussion of the results that a preliminary re-appraisal of tonometry; a critical examination of some of the papers cited supporting tonometer use; and the importance of sleep dynamics in future research needs to be addressed. A proposal for future research is presented, before considering the experimental results.

Grolman *et al* (1990) comment that Goldmann has, by consensus, become the standard by which other tonometers are graded. That does not suggest that the Goldmann is a perfectly accurate and repeatable reference standard. All instruments, including the Goldmann, show variability. Kass (1996), Thorburn (1978) and Grolman *et al* (1990) report ranges of Goldmann repeatability of up to 6.2 mmHg.

Goldmann tonometry measurements are estimates based on the Imbert-Fick law (Schottenstein 1996), which states that 'the pressure inside a sphere is roughly equal to the external force needed to flatten a portion of the sphere divided by the area of the sphere which is flattened'. The term 'roughly' is not defined but does suggest some variability in the law. It may allude to the fact that the pressure inside a sphere that has been compressed is higher than the pressure uncompressed. The act of applanating the sphere increases the pressure inside. The larger the area of applanation, the larger is the artificial change in internal pressure (Schmidt 1959). Practical application of the law is further compromised by the fact that it only applies to surfaces that are perfectly spherical, dry, flexible, elastic and infinitely thin (Schottenstein 1996). Schottenstein goes on to name a number of variables necessitating the addition of compensation factors to the original formula. Variables such as the force tending to push the applanating surface away from the eye and central thickness of the cornea need to be compensated for in the equation but can not be considered constants.

Is, or was, the Goldmann Applanation Tonometer a worthy 'Gold Standard' considering the formulaic compensations required, coupled with operator variability when using the instrument (Kass 1996, Thorburn 1978, Grolman *et al* 1990)?

At some point the Schiotz was presumably the reference standard. No mention of a predecessor to the Goldmann as 'gold standard' can be presented. However,

Katavisto (1964) states that impression tonometers such as the Schiotz were in much more general use than any other type at that time, while Starrels (1979) also remarks that Schiotz was, in the past, the most widely utilized pressure sensor. Even at the time of this paper, Starrels lists advantages of Shiotz as its' familiarity, low cost, portability and ease of operation. So what evidence had to be presented to change the general consensus and accept Goldmann as the reference?

Goldmann's first paper describing his refined version of an applanation tonometer appeared in 1955 (not cited). Schmidt (1959, 1960) describes the use of this new instrument and explains why it is superior to the Schiotz. Schmidt argues that the accuracy of the Schiotz depends on 20 different dimensions and characteristics, as well as the natural physiological conditions of the eye. He goes on to explain that applanation tonometry itself is not superior to indentation. The Maklakoff applanation tonometer for instance, available for considerable time prior to the Goldmann, did not supplant the Schiotz as the instrument of choice. Schmidt describes the refinements made by Goldmann. Apart from friction between moving parts the Goldmann tonometer had only two points where the instrument itself could affect the reading :

1. Precision of manufacture of the prism
2. Accuracy of the balance, which measures the force required to produce the specified amount of applanation.

Schmidt (1959, 1960) convincingly argues that the Goldmann tonometer is a superior instrument to all previous applanation tonometers, as well as the Schiotz. The author was only considering the application of the technique and did not consider operator variability, a totally objective alternative not being available in the 1950s. For all the refinements incorporated in the Goldmann Schmidt still acknowledges that the ideal tonometer would be a compensated membrane manometer.

The Goldmann was the result of an obviously methodical and analytical assessment of the variables involved in intraocular pressure measurement in the 1950s. Variables that could be controlled or eliminated were - machine variables were reduced from 20 with the Schiotz to 3 (Schmidt 1959, 1960). Individual physiological variability could be normalised but not eliminated. Likewise, frictional interactions within the instrument while minimised could not be eliminated, nor could operator variability.

Would current technology allow any improvement on the Goldmann? Non-contact tonometers certainly are as susceptible to physiological variability of the subject as the Goldmann. However, solid-state electronics allow virtually frictionless operation of modern tonometers and the automation removes operator variability. In principle it should be possible to make fundamental improvements in the measurement of intraocular pressure.

Grolman *et al* (1990) for instance suggests that the Reichert XPERT non-contact tonometer could become the 'reference' for many clinicians. Just as Schmidt did in 1959, while advocating the possible superiority of a newer, refined instrument, the authors maintain that the only error free reference standard for tononmeters would be a manometer. Would this be impractical? At the research and development level, when there is ambiguity about the validity of many tonometric measurements, it would seem a valid concept to consider. Rizq, Choi, Eilers, Wright and Ziaie (2001) took this approach when assessing the accuracy and validity of a micro sensor tonometer surgically implanted under the sclera, in direct apposition with the choroid. These researchers were developing a fundamentally different method of tonometry, one bypassing and eliminating the physiological variability between human eyes. These authors compared their results to manometer readings of cadaver eyes, it would have been counterproductive to compare this technique to the Goldmann, the readings from which are confounded by corneal variability.

Not withstanding these arguments Fisher *et al* (1988), Moseley *et al* (1989) and Vernon (1989) report that the Pulsair's clinical trials and factory calibration were based on a series of Goldmann measurements. Vernon (1989) also reports that according to manufacturers data the calibration against Goldmann is over a range of 5 to 50mmHg. It can be argued that since instrument evaluations are predominantly concerned with assessing a new tonometer as a clinically viable tool, comparison to the Goldmann is acceptable since it is the instrument of choice in ophthalmology clinics and as such constitutes the final arbiter for accepted pressure.

However, if, due solely to historical precedent, manufacturers continue to calibrate and compare to the Goldmann then no fundamental improvements in our ability to refine accuracy of IOP measurements can be expected.

Until such alternatives are considered, the suitability of the Pulsair 3000 must be based on traditional Goldmann comparisons.

Evaluating the Pulsair 3000 against the Goldmann Reference Standard

How accurate is the Pulsair 3000 under these experimental conditions?

When critiquing papers assessing any tonometer, it is important to bear in mind that the authors are comparing one technique with innate variability to another with innate variability. To complicate interpretation of comparisons many authors seem to emphasise inappropriate statistical concepts or misinterpret statistical results leading to spurious claims of instrument accuracy.

Many authors researching intraocular pressure quote correlation coefficients with Goldmann tonometry as the sole rationale for accepting the tonometer used in their protocols (Wildsoet *et al* 1993, Frampton *et al* 1987, Brown *et al* 1988a). Other authors comparing different instrumentation also quote correlation coefficients (Sorensen 1975, Moseley *et al* 1989, Vernon 1989,

Moseley, Thompson, Deutsch, Misson, Naylor, Tan-Yee, Taylor & Fielder 1993, Wingert, Bassi, McAlister & Galanis 1995, Parker *et al* 2001). While these authors confer more emphasis on other statistical results, the inclusion of correlation coefficients does infer significance. High correlation simply suggests that a relationship between the two techniques exists but does not necessarily confirm agreement (Bland & Altman 1986).

Correlation coefficients become singularly important when they indicate a lack of correlation. Since comparisons are made between techniques that purport to measure the same physiological phenomenon, a lack of correlation suggests that absolutely no relationship exists and that the compared techniques are, in effect, measuring different things. Comparing non-contact tonometry with Goldmann, Sorenson (1975) found no correlation for intraocular pressures over 35mmHg, making further statistical assessments of agreement and repeatability of little worth.

The best index of an instrument's reliability is the standard deviation of differences of matched pairs of readings (Grolman *et al* 1990). Factors affecting the standard deviation would include any protocol item that could contribute to measurement variability. Physiological factors, Goldmann tonometry and its' operators, the new tonometer and its' operators, IOP time dependence and the effect of one measurement upon another, are all cited by Grolman and associates (1990) as inherently affecting the standard deviation. The authors conclude that a standard deviation is actually a measure of the study's aggregate variability.

Sorensen (1974), Fisher *et al* (1988), Moseley *et al* (1989) and Moseley *et al* (1993) attributed all variability to the NCT. Bland and Altman (1986) comment that this creates a statistical artefact. A standard deviation thus calculated would suggest higher variability for the instrument being assessed.

Bland and Altman (1986) suggest that since it is highly unlikely that either instrument can be assured to be perfectly accurate, a comparison to the mean differences between the two methods is the best estimate of the true figure that

can be made. Mackie, Jay, Ackerley and Walsh (1996) used this analytical technique to compare the Pulsair 2000 to the Goldmann standard. These workers calculated two standard deviations from the mean difference to be ±7.12mmHg and reported that 95% of Pulsair 2000 readings fell within this range. These authors suggest that this confirms satisfactory agreement. Since, by definition, 95% of readings fall within two standard deviations, if gaussian distribution is assumed (Bland & Altman 1986), then this assumption is potentially spurious. Grolman *et al* (1990) state that the ISO criterion for standard deviation for certification and verification of tonometers is 2.5mmHg and Bland and Altman (1986) stress that the acceptable range of variability between two instruments should be set by clinical requirements. Consequently a 95% confidence range of ±7.12mmHg would not indicate acceptable accuracy.

Parker *et al* (2001), comparing the Pulsair 3000 to the Goldmann standard also misinterpret 95% confidence limits. These authors actually state that '95% of the differences should be less than two standard deviations from the mean difference in order for the instrument to be accepted'. While these authors misinterpreted the Bland and Altman strategy their results did show a range of only ±2.24mmHg. So while the authors' logic was flawed the results do suggest the Pulsair 3000 shows acceptable agreement with the standard.

Bland and Altman (1986) and Grolman *et al* (1990) explain that narrow sample distributions severely limit the accurate plotting of the regression line. Good correlation may still be demonstrated but the line of equality indicating agreement must have a slope of 1, which would be less likely with a narrow sample range. Augsberger and Alexander (1982) compared six different tonometers but measured tensions over a range of only 3.46 mmHg, and reported slopes of regression lines varying from 0.66 to 0.89. These slopes do not necessarily imply a level of agreement but rather reflect the narrow range of tensions sampled.

A final point when interpreting clinical papers is at what point should stated statistical significance be accepted. Mackie *et al* (1996) report a correlation

coefficient between Pulsair 2000 and Goldmann of 0.82 as good. Is it? No references supporting these levels as satisfactory are cited, but Elliott (1998) reports that 0.90 is the minimum requirement for clinical tests.

Wingert *et al* (1995) comparing five different tonometers to the Goldmann report a range of correlation coefficients from 0.61 to 0.75 (the latter being the Pulsair) as highly significant. High significance was also placed on the regression lines, with slopes ranging from 0.48 to 0.86 (Pulsair slope 0.60) and Y intercepts from 4.67 to 10.67 (Pulsair 7.21). Since the perfect line of agreement would have a slope of 1.0 and a Y intercept of zero (Grolman *et al* 1990) these results do not suggest good agreement between any tonometers.

As a screening tool, agreement with minimal bias to the Goldmann standard and the instruments' repeatability are important in ensuring sensitivity and specificity of referral. Fortunately equivocal findings can be checked by other techniques to refine any referral or ongoing management.

Within this experimental setting we are much more concerned with how the tonometer represents relative changes in pressure across the sample range and the repeatability of the measurements suggesting those changes. Relative change is not affected by small degrees of bias as long as it is uniform across the sample range. Individual variability such as corneal thickness, which would affect the accuracy of absolute pressure readings, will also be of no concern in this study for identical reasons.

In this research pressures from 7 to 28mmHg were sampled. So does the Pulsair 3000 fulfil its' experimental role over this range?

The papers comparing the Pulsair family of machines to the Goldmann cited in this document present lines of regression with slopes ranging from 0.60 (Wingert *et al*), through 0.7392 (Brencher *et al* 1991), 0.75 (Moseley *et al* 1989), 0.95 (Moseley *et al* 1993, Fisher *et al* 1988) to 1.064 (Mackie *et al* 1996). These papers also report positive Y intercepts ranging from 0.00 to 7.21.

While not convincing statistics when assessing the instruments for clinical accuracy, they do increase the significance of the sleep induced IOP peaks demonstrated in this study, since they indicate pulsairs generally underestimate high pressures and overestimate lower. Bonomi *et al* (1991) also infer there is good repeatability of the pulsair (a 3000 predecessor) for pressures above and below 24mmHg.

Parker *et al* (2001) specifically assessing the Pulsair 3000 reports a standard deviation from the Goldmann of only 1.1179 and a 2 standard deviation range from the mean difference of the two techniques of only 2.24 mmHg. The range of tensions checked was10 to 44 mmHg and while the regression equation was ignored visual inspection of the graph suggests a slope approximating 1. Good repeatability for the Pulsair 3000 across a pressure range of 9 to 26 mmHg was demonstrated by McCaghrey and Matthews (2001), who found that when 3 readings were averaged 96% of the figures fell within a 1 mmHg range of the machine standard (average of 4 readings).

The experimental requirements were met by the Puslair 3000 measurements. The change in bias across the pressure range actually emphasising the sleep induced peaks noted. However, future research would benefit from a measurement technique less open to conjecture.

Implications of Sleep Depth and Sleep Disturbance on Data Collection

Buguet, Rivolier and Jouvet (1987) comment that sleep disturbances are common in unusual environments. Agnew, Webb and Williams (1966) also describe the ‘first night effect’; electroencephalographic tracings demonstrated significant changes to sleep patterns of subjects during the first night of an experimental study, with normalisation rapidly returning by the second and subsequent nights. Blois, Feinberg, Gaillard, Kupfer and Webb (1983) describe differences in sleep patterns between young and elderly subjects, as well as between healthy subjects and those with certain pathological conditions.

Earlier papers specifically investigating IOP and sleep (Frampton *et al* 1987, Brown *et al* 1988a, Brown *et al* 1988b, Ido *et al* 1991 Wildsoet *et al* 1990, Wildsoet *et al* 1993) made no attempt to pre-assess the subjects for sleep patterns, habituate the subjects to the sleeping conditions or attempt to quantify sleep depth during the experiment. Some authors comment on sleep patterns, Wilensky (1991) stated that all subjects remarked on not feeling as if they slept well, while Ido *et al* (1991) reported having to physically wake volunteers from deep slumber.

Attempts to standardise and control sleep patterns have been advocated and used by other researchers. The protocol used by Birchley *et al* (1990) ensured no subjects were shift workers or on permanent night duty. Buguet *et al* (1987) report Antarctic sleep studies using questionnaires to pre-assess each subjects perceived sleep quality. Blois *et al* (1983) give examples of the types of questions used in a questionnaire assessing sleep patterns in the elderly. In all the studies led by Liu (Liu *et al* 1998, Liu *et al* 1999a, Liu *et al* 1999b, Liu *et al* 2002, Liu *et al* 2003a, Liu *et al* 2003b) the subjects were selected for having regular daily sleep of approximately 8 hours, although the papers did not report formalised questionnaires. The subjects were also instructed to maintain daily 8-hour sleep periods, with lights off, for seven days prior to the laboratory data collection.

Racz *et al* (1996) accumulated a 24-hour pattern over a 5-day collection period. Each subject was woken only once per night, but at different times on successive nights. This simple technique does reduce interference with sleep and also minimises any ‘first night effect’, although it assumes a regular sleep rhythm for each individual. The normalisation of sleep patterns after the first habituation night reported by Agnew *et al* (1966) would support the use of this technique. Blois *et al* (1983), purely researching sleep patterns using electrophysiological techniques, took traces over two nights and after one habituation night.

Other researchers such as Birchley *et al* (1990) and Buguet *et al* (1994) used polysomnographic techniques to definitively quantify sleep depth before waking the subject to take the IOP readings.

The importance of grading sleep depth was illustrated with these experimental procedures. Reliance on subjective impressions as Wilensky (1991) and Ido *et al* (1991) did, are not suitable if sleep induced IOP peaks specifically, is being investigated. It is imperative that authors not only record the time of measurement but also the sleep depth at waking. The time delay before any measurement is recorded is also important since a rapid return to normality has been demonstrated (Brown *et al* 1988b, Zeimer 1990). Much of the conflict in the literature concerning circadian variation in IOP could well depend on these factors.

Future Resolution of the Sleep Induced IOP Spike Conundrum.

Resolution may not be until an alternative method can be developed that is able to measure IOP continuously and accurately without disruption to daily activities or sleep patterns.

Schottenstein (1996) did stress that a tonometer is needed that can monitor pressure continuously for hours or days; various devices are mentioned but dismissed as showing no clinical usefulness.

McLaren, Brubaker and FitzSimon (1996) and Schnell, Debon and Pericot (1996) implanted telemetric pressure transducers in rabbits. The entire system was bulky and required quite invasive surgical procedures with occasional surgical mishap. The transducer catheter entered the anterior chamber and careful monitoring for inflammatory responses was required. Once recovered from the surgery the rabbits showed normal behaviour patterns, but the transducer range was very limited and battery life short.

Rizq *et al* (2001) describe a technique to insert an IOP sensor via a trephine through the sclera and placed in direct contact with the choroid. This study used cadaver eyes but proved that surgically implantable microsensors are feasible and accurate. The conclusion was that this procedure could be used to monitor patients with hitherto difficult to manage glaucoma. As a research tool this could be more valuable in enlightening us as to why some patients have difficult to manage glaucoma.

There is a significant gulf between a feasibility study using cadaver eyes and proceeding on to live, human trials. However, at least at a research level this may suggest a way forward for a more critical evaluation of the nature of IOP variations. While the author has reservations about animal studies, the use of implantable microsystems as described by Rizq *et al* (2001) on higher primates, with similar nocturnal sleep cycles to humans could be an important interim step before human implantation is practicable.

DISCUSSION

Logistical and financial constraints limited the potential scope of this current research.

Time constraints of organising a weekend campsite meant that only one data collection period was available. No sleep habituation was possible, with ‘first night’ effects being likely. The sleeping accommodation was relatively uncomfortable, certainly unfamiliar and did not encourage deep, undisturbed sleep patterns.

While sleeping conditions were poor, ensuring deep sleep was enhanced by the nature of the research design. Since it was postulated that IOP peaks are sleep induced the subjects were allowed to sleep at any time, habitual sleep patterns

being deliberately avoided. No attempt to manipulate sleep length was made either. This worked extremely well for the younger subjects who only went to bed when forced by sheer fatigue. A very dramatic example of this was 'Subject 8' (Fig 8) aged 15 who did not sleep till 2.00pm in the latter stages of the data collection period. The graph for 'Subject 8' demonstrates the marked IOP spike at 3.00pm during a very short sleep episode. At this point the subject had been awake continually for about 30 hours, from the morning before data collection started.

The adults, however, did not sleep well. The relatively uncomfortable sleeping conditions coupled with the responsibility of supervising the younger volunteers made sleep very difficult.

Regardless, the results lend further strong support that predictable sleep induced peaks in IOP exist, at least with normal subjects. While the grading system adopted for this research was necessarily simplified to suit the resources available, the results also suggest that sleep depth is an important factor in inducing the IOP peaks.

A possible implication with the sleep grading system adopted in this research is the suggestion that Slow Wave sleep and REM sleep have differing IOP responses. Buguet *et al* (1994) found tensions to be highest during slow wave sleep (17mmHg, n=74) but on average 1 mmHg lower during REM sleep (16 mmHg, n= 102) and this was found to be significantly different. Birchley *et al* (1990) however, while reporting the mean rise in IOP during 'Slow Wave' sleep to be 1.63mmHg higher than during 'REM' sleep did not find the difference to be significant. This data set was collected from only nine individuals making the statistical techniques far less powerful. In this current study no differentiation between REM and Slow Wave sleep was possible (both were graded as level 3 – Deep Sleep).

Apart from Subject 14, every volunteer assigned a sleep grade of 3 showed a significant rise in IOP during sleep, regardless of when during the nyctohemeral period that sleep period occurred. No discernable pattern was evident for the three subjects who remained awake and the nyctohemeral plots of subjects who experienced only 'light' sleep do not show a clear visual separation of the 'Awake' and 'Asleep' readings.

Results in Context with Previous Work

Whereas previous studies on this topic have maintained nocturnal sleep patterns, this research deliberately disrupted sleep schedules. Regardless of time of sleep, pressure rises were recorded if the subject's sleep depth was graded as 'Deep'.

However, the protocol and data collection techniques did not allow identification of general trends but rather demonstrate individual variability.

Liu *et al* (1998) described increasing IOP throughout the nocturnal sleep period for healthy young subjects with a peak at 5.30am. This timing of the IOP peak was also confirmed for untreated glaucoma patients, with habitual awake/sleep posture (Liu *et al* 2003a). Frampton *et al* (1987), using young healthy subjects, found a progressive increase in IOP during sleep and Wildsoet *et al* (1993) who investigated both normal and glaucomatous subjects detected the same trend in both sample groups. Brown *et al* (1988a) reported a significant rise in IOP within 30 minutes of onset of sleep but found a continuing rise throughout the 4-hour sleep period.

The subjects in this experiment did not all enjoy extended periods of sleep. Four subjects (8,16,17,20) had extremely short sleep periods and all showed rapid spikes. This supports the rapid increases reported by Brown *et al* (1988a) but no inference about continuing rises can be made. Subjects 10,11,19,23,24,25 did show sustained rises in recorded IOP during sleep periods with the highest pressures being immediately prior to waking, but others (9,12,13,15,18,21,22)

demonstrated rises followed by a slight fall before waking. All these tensions were recorded when the subjects' sleep was graded as 'Deep', but without a more objective method of grading, these variations could be due solely to undetected changes in sleep patterns.

Importantly the studies indicating general trends throughout the sleep period, also dictated specific sleep periods for the subjects. This allowed composite curves to be generated from all the subject data. Individual variations, as found in this study, would be masked by this technique.

Some conflict exists in the literature when crucial sub-populations have been investigated, in particular the elderly and glaucoma patients.

Liu *et al* (1999b), investigating elderly patients demonstrated an IOP peak much earlier in the sleep/nocturnal period. Buguet *et al* (1994) on the other hand presented data suggesting that younger subjects show rapid IOP rises after sleep onset while the elderly had more progressive increases.

'Sleep Latency', the delay before onset of sleep, 'Waking Latency', a measure of sleep stability and the 'Efficiency Index', ratio of total sleep time to time in bed, have all been demonstrated to decrease with age (Blois *et al* 1983). It is highly possible that elderly subjects also demonstrate more pronounced 'first night' effects. Neither Buguet and associates (1994) nor Liu and co workers (1999b) allowed the subjects a habituation night and both groups woke the subjects often during the sleep periods. The conflicting results for ageing patients could be due to this groups' intolerance to sleep disruption. Buguet and co workers (1994), having access to polysomnography, did note that the elderly subjects had more difficulty falling back to sleep after measurements.

The results of this current research also support this notion, with the older subjects being less likely to fall promptly back to sleep.

Disruption of conventional sleep patterns and depths were particularly evident with the adults, only 50% (4 individuals) of the subjects over 20 years of age having sleep depth graded as 'Grade 3 – Deep'. The younger subjects generally slept better with 82% (14 individuals) of volunteers under 20 years of age having sleep stages classified as 'Deep'. One of the adults deliberately remained awake throughout the data collection period to assist in the experiment.

It is possible that the very early peak in IOP (11.30pm) noted by Liu *et al* (1999b) for elderly subjects represents the initial, rapid rise reported by several groups (Frampton *et al* 1987, Brown *et al* 1988a, Wildsoet *et al* 1993, Buguet *et al* 1994), with any further accumulative rises in IOP being negated by the repeated sleep disruption during the nocturnal measurements. Since Liu *et al* (1999b) did not have access to objective measures of sleep depth this is speculation, but discrepancies between the Liu *et al* and Buguet *et al* results for elderly subjects highlights the need for a more robust experimental protocol to ensure sleep disruption is minimised and sleep depth is quantified.

Can it be assumed that glaucoma patients and suspects, who generally will be older than the subjects in this experiment, demonstrate similar sleep related nyctohemeral curves? If they do show variability does this reflect true differences in their pressure profiles or do they respond differently to experimental conditions?

Most recent research seems to support the concept of sleep induced IOP peaks for glaucomatous and elderly patients (Wilensky 1991, Wildsoet *et al* 1993, Liu *et al* 2003a, Zeimer *et al* 1990, Buguet *et al* 1994, Liu *et al* 1999b).
Orzalesi and associates (2000) however, suggested an IOP trough at 3.00am followed by increasing pressure through the remaining sleep period with a peak at 9.00am.

More at odds with the general consensus are the results presented by Noel *et al* (2001). These authors found pressure troughs at 3.00am and peaks 8 hours later for untreated and treated glaucoma patients, while the healthy controls

demonstrated a peak at 3.00am. This paper warrants particular comment. The glaucoma patients were slightly older (mean 35 years, range 20-45) than the healthy subjects (mean 24.5 years, range 20-30). The subjects were woken hourly but polygraphic traces did not show a difference in sleep response for the older group. The authors report that sleep period, total sleep time and sleep latency were similar between healthy and glaucomatous subjects. Data sampling was identical for healthy volunteers and glaucoma patients. These authors remark that the most striking result was the apparent reversal of the 24-hour pressure profile for glaucoma subjects. Regardless of that conclusion the authors also noted that whenever a subject napped during the day, IOP spikes were observed, regardless of sleep duration. Further, Noel and associates remark that, for healthy subjects, tensions are highest during 'slow wave sleep', which occurs at the beginning of the sleep period. The authors argue this explains the rapid rise at sleep onset. While no comment is made this would also explain the IOP spikes observed for both healthy and glaucomatous eyes when the subjects napped during the day. Tensions during 'REM sleep' did not differ greatly to awake pressures for either glaucomatous or healthy subjects - tensions during 'light sleep' were equally equivocal. It seems highly possible that the researchers were not sampling 'slow wave sleep' for the glaucoma group apart from when they were allowed to sleep, without encouragement, during the day.

One suggestion is that researchers are not sampling the same phenomenon. Noel *et al* (2001) suggested a daytime peak in IOP for glaucoma patients but noted a sleep associated IOP spike during daytime naps. Wilensky (1991) investigating a variety of parameters affecting IOP, reported that 'daytime curves' (pressures greatest between 8.00am and 2.00pm) were most prevalent, and yet when specifically assessing the affect of sleep on IOP confirmed tension spikes during sleep episodes.

Until a far more robust and unified methodology is considered, the validity of results will be compromised by the possibility of confounding variables. Only some of these variables have been adequately explained.

Some Confounders and Artefacts Explained.

Since it is impossible, with current technology, to sample the pressures without actually waking the patient, the possibility that the sleep-induced peaks in IOP are artificial has to be considered.

One concern was the possibility that closed lid induced corneal oedema could increase corneal turgidity causing an apparent rise in IOP. This was discounted by Frampton *et al* (1987), who induced corneal oedema in volunteers using low water, thick HEMA contact lenses and found that corneal oedema induced during sleep was not of the order that could explain the increases in IOP recorded.

Posture and light levels were other variables complicating the experimental picture. Frampton *et al* (1987), Wildsoet *et al* (1990) and Liu *et al* (2003b) confirmed that while head down posture does cause a significant increase in IOP it does not correspond to the rise elicited during sleep. Light levels and lid pressure on the globe during sleep have also failed to fully explain the sleep-induced elevations in IOP (Wilsoet *et al* 1990, Wildsoet *et al* 1993, Liu *et al* 1999a). Miller (1967) measured pressure on the globe and found that gentle lid closure, as in sleep, caused a lid pressure on the eye of only 3.2mmHg, compared to 10.3mmHg during 'deliberate blinking', which Miller suggests is akin to normal reflex blinking.

The cumulative effect of closed lid corneal oedema and globe pressure, supine position and darkness, likewise could not emulate the magnitude of IOP elevation induced during sleep (Frampton *et al* 1987, Wildsoet *et al* 1990).

Hard, forceful blinking creates a much more significant lid pressure on the globe of up to 51mmHg (Miller 1967). Since IOP elevations were recorded

specifically for subjects being roused from ‘Deep’ sleep and not lighter sleep, the possibility that vigorous lid flexure is a feature more specific to arousal from deeper sleep states needs to be briefly considered.

The lid pressures of 51mmHg recorded by Miller were measured in seconds. While this is not a measure of IOP, any related rise in tension caused by compression would dissipate immediately on pressure release as the globe volume normalised. The IOP elevations recorded after waking show much longer recovery times, 404.8 seconds (Brown *et al* 1988b). Thus pressure rises due to tight lid flexure during waking could not explain the IOP rises recorded.

Intraocular Pressure Homeostasis.

Does the dynamics of aqueous flow and homeostasis suggest that a sleep induced rise in IOP is a bona fide phenomenon?

Intraocular pressure is governed by the balance of aqueous inflow versus resistance to aqueous outflow and episcleral venous pressure (Ericson 1958, Takeda & Azuma 1978). Pressure differentials between the aqueous outflow facilities and the episcleral veins will influence the intraocular pressure, low systemic blood pressure resulting in a lowered intraocular pressure (Nilsson & Bill 1995). Consequently, the nocturnal dip in systemic blood pressure reported by Graham, Drance, Wijsman, Douglas and Mikelberg (1995) and Hayreh, Zimmerman, Podhajsky and Alward (1994), coupled with the reduced aqueous inflow during sleep reported by Ericson (1958) and Reiss, Lee, Topper and Brubaker (1984) would make tension troughs during sleep expected rather than the spikes reported in this and other studies.

Brown and associates (1988a) stress that the fluorophotometric techniques used by Ericson (1958) and Reiss *et al* (1984) are only sensitive to changes in aqueous flow over hours and may not be sensitive enough to detect the short-term fluctuations that could cause changes in IOP. These authors also suggest

that without an understanding of the balance of all the variables the resulting IOP cannot be predicted.

However, unless alternative mechanisms become evident the reduced aqueous inflow coupled with a nocturnal dip in systemic blood pressure, leaves only resistance to outflow as a variable that could explain the rise in IOP noted.

If sleep related IOP spikes are confirmed, future research needs to demonstrate a link between the IOP elevations and at least one of the mechanisms contributing to its' control. Increased resistance to outflow is the most likely mechanism to explain the phenomenon.

Waking Related Instantaneous IOP Spikes.

Wilensky (1991), while presenting data supporting IOP rises during sleep in both normal and glaucomatous patients, questioned whether this could be an instantaneous elevation associated with waking up. The proposition, passed to Wilensky via personal communication is that an acute elevation in systemic blood pressure at waking causes an increased volume of blood to be pumped into the eye which then rapidly dissipates.

Instantaneous rises in IOP due to equally momentary changes in systemic blood pressure seems unlikely. To the author's knowledge, however, this proposition has not been considered by other researchers and if it does exist it makes the search for other mechanical, neural or chemical mediators for the sleep induced elevations in IOP academic.

So instantaneous systemic hypertension at waking could precipitate the apparent rises in IOP, but apart from the possibility being mentioned by Wilensky (1991) no evidence is apparent. Nocturnal hypotension is the general trend as reported by Staessen, Fagard, Lijnen, Thijs, Van Hoof and Amery (1991) who conducted meta-analysis of 23 studies. Analysis of general trends however, could miss

isolated episodes. Hayreh *et al* (1994) measured systemic blood pressure every 20 minutes while the subjects slept and every ten minutes while awake. With measurements that frequent, hypertensive spikes would be expected to be evident in a proportion of the 166 volunteers. None were mentioned but the authors do report removing outlying results, which they imply could occur due to inadvertent arm flexure at measurement or due to transient emotional or physical change. This fact could be significant. Graham *et al* (1995) recording blood pressure every 30 minutes throughout the 24-hour period also failed to report any hypertensive spikes at waking but also adhered to the outlier rejection criterion.

Pickering (1991), while cataloguing a variety of activities and states that can induce rapid hypertensive elevations in systemic blood pressure above normal levels, does not mention waking in this context. The author does remark that blood pressure rises rapidly at the point of waking but only as nocturnal hypotension returns to normal daytime levels. Abnormal hypertension at waking that could induce the elevation in IOP, is not demonstrated.

Buguet *et al* (1994) discounted the possibility of instantaneous changes to IOP on waking. These authors suggest that the time of recovery of normal IOP levels reported by Brown *et al* (1988b) as 404.8 seconds from waking is too long. The same researchers also note that they found a difference in pressure when patients were woken from REM sleep compared to Slow Wave sleep. If IOP spikes were due solely to an independent mechanism related to waking, then this difference is unlikely to manifest.

Wilensky (1991), as an experimental subject as well as author, made the observation that by the time the technician had approached him, administered anaesthetic and recorded tensions he had been awake some time. Wilensky offers this as implying that a systemic hypertensive episode should have subsided.

The possibility of systemic hypertensive episodes needs to be clarified.

Possible Chemical Mediators.

Chemical mediators have been demonstrated to affect IOP.

Melatonin, secreted by the pineal gland, appears to be a sleep regulator (Birkeland 1982). Its' circadian rhythm helping maintain the normal diurnal/nocturnal wake/sleep cycle, while episodic elevations associated with mid-sleep awakenings help re-establish homeostasis. Birkeland reported that circulating melatonin is generally highest during the wake state and lowest during REM sleep.

Samples, Krause and Lewy (1998) suggested that high serum melatonin levels correspond to lowest IOP but their subjects were awake throughout data collection. The authors also demonstrated that oral administration of melatonin caused a significant decrease in IOP. The Samples and associates results would suggest that an IOP rise during sleep could be expected as melatonin levels fall as sleep is established (Birkland 1982).

Other studies (Chiou & McLaughlin 1984, Liu & Dacus 1991), using rabbits, suggest that melatonin increases IOP. Samples *et al* (1988), report that in animals melatonin regulates seasonal and breeding behaviour, whereas Birkeland (1982) reports that in humans it is a sleep-regulating hormone. Since the role of melatonin seems to vary between species, then its' effects, especially in a nocturnal species, may vary as well. Another consideration about the conflict in the literature would be the possibility that different concentrations have different effects. Prostaglandin analogue drugs are a case in point, where dosage affects the response. Camras (1996a) reports that injection of high doses of these drugs into rabbit eyes induced significant rises in IOP, rather than the desired reduction.

Birkeland (1982) found that if lights were left on during sleep, within a week the melatonin rhythm reversed. As a sleep regulator for a diurnal species,

responding to changes in light may constitute a bid to force the body to readjust its' sleep pattern to correspond to the diurnal/nocturnal cycle.

This inertia of the body's habitual melatonin rhythm to readjust to a fundamental environmental change appears in conflict with the findings of this study, which demonstrated rapid changes in IOP during non-habitual sleep episodes. However, sleep deprivation has been shown to increase melatonin secretion and melatonin outbursts are associated with extraordinary waking events (Birkeland 1982). Rapid rises in IOP recorded for subjects who only achieved the briefest of sleep periods during daylight, but after significant sleep deprivation would correspond to a reduction in plasma melatonin levels as sleep is established. Sudden awakening would generate a melatonin outburst as the body attempts to re-establish sleep.

A complication to this pharmacological causation model is that melatonin is also synthesised locally in ocular tissues (Wildsoet *et al* 1990) and interpretation based solely on plasma melatonin levels may be excessively simplistic. The model does warrant further investigation as its' proposed sleep regulatory role fits the findings of this study very well. However it seems unlikely that intraocular pressure homeostasis is maintained by a sleep regulatory hormone which, when levels fall during slumber, allow IOP to rise to potentially pathological levels.

Cortisol is another endogenous chemical demonstrating a circadian rhythm in plasma concentrations. Secreted by the adrenal medulla it is related to the corticosteroids, which have a well-documented side effect of increasing IOP (Skuta & Morgan 1996, Wildsoet *et al* 1990). Becker (1965) demonstrated that individuals with primary open angle glaucoma show dramatic rises in IOP in response to topical corticosteroids; tensions over 31mmHg were recorded and the authors suggest that further elevations exceeding 40mmHg could have been elicited if allowed.

Boyd and McLeod (1964) and Weitzman, Henkind, Leitman and Hellman (1975) demonstrated that plasma cortisol levels are lowest during the earliest part of the nocturnal sleep period. Levels rise throughout nocturnal sleep and peak at about 8am. No inference can be made about cortisol levels when the subjects have abnormal sleep patterns. Both research groups, while finding cortisol levels rise during sleep, found nocturnal troughs for IOP. Weitzman and associates do comment that the rise in cortisol levels during sleep should suggest an IOP rise in the same period. Studies since these were published would suggest that this may in fact be the case.

Cortisol seems a more likely candidate than melatonin for explaining the observed rise in IOP during sleep. Firstly, cortisol levels actually rise during sleep whereas it is the absence of melatonin that correlates to elevated tensions. Secondly, corticosteroids seem to affect IOP by increasing resistance to outflow within the trabecular meshwork (Skuta & Morgan 1996, Boyd & McLeod 1964). This is highly significant since the rhythm of two of the three components governing IOP homeostasis, aqueous inflow and episcleral venous pressure (Ericson 1958, Takeda & Azuma 1978), predicts a reduced IOP during sleep. Only increased resistance to outflow could explain the sleep induced IOP spikes reported.

Greater significance could be placed on cortisol if plasma levels could be demonstrated to vary rapidly in response to irregular, short or disrupted sleep patterns. This would link with the IOP spikes highlighted in this study, being found regardless of time or duration of sleep. If the habitual circadian rhythm of plasma cortisol shows inertia to changes to sleep patterns, then it must be discarded as a candidate.

IOP Spikes and Prostaglandin Analogue Use.

Can the results from these experiments, using non-glaucomatous subjects, support the use of prostaglandin analogue drugs for the treatment of chronic

open angle glaucoma, especially when such patients are more likely to be elderly? There is now a great deal of evidence in the literature supporting the existence of sleep induced rises in IOP. The trend has been demonstrated with healthy (Frampton *et al* 1987, Brown *et al* 1988a, Brown *et al* 1988b, Birchley *et al* 1990, Wildsoet *et al* 1990, Buguet *et al* 1994, Liu *et al* 1998) as well as glaucomatous eyes (Wilensky 1991, Wildsoet *et al* 1993, Liu *et al* 2003a, Zeimer *et al* 1990) and ageing eyes (Buguet *et al* 1994, Liu *et al* 1999b). These studies all used habitual nocturnal/diurnal sleep/wake cycles. In the current work IOP spikes were elicited regardless of time of sleep. Since there is a good deal of evidence that glaucomatous eyes demonstrate equivalent sleep related rises in IOP with nocturnal sleep, it is reasonable to assume that IOP spikes could be expected with glaucomatous eyes regardless of time of sleep. Noel *et al* (2001) while suggesting pressure troughs at 3.00am, still reported IOP spikes for glaucoma patients during daytime sleep episodes.

The question of which IOP value is most prognostic for glaucomatous progression, mean, peak, trough or range (Wilensky 1991), is still debatable. However there is significant evidence that peaks are critical (Asrani *et al* 2000, Zeimer *et al* 1990, Zeimer *et al* 1991) and intuitively (Gelatt & MacKay 2001, Kontas *et al* 1999, Zeimer 1990) IOP spikes should be more damaging. Certainly a drug therapy that could effectively reduce tensions throughout the nyctohemeral period but also dampen peaks would logically show the highest efficacy in slowing progression of glaucoma.

Consequently the presence of sleep-induced peaks in IOP does support the conventional evening administration of prostaglandin analogues but with certain caveats. Maximal effect of prostaglandin analogues appears to be between 8 and 12 hours after instillation (Alm & Villumsen 1991, Hotehama & Mishima 1993, Hotehama *et al* 1993 and Villumsen & Alm 1992, Product Monograph – Pfizer Canada 2004). Since pressure appears to rise rapidly after the onset of sleep and may continue to rise throughout the sleep period, the optimal drug administration point for patients with habitual, nocturnal sleep patterns should be about 8.00pm.

The Pfizer product monograph (Pfizer Canada 2004) states : 'One drop of Xalatan should be dropped into the affected eye(s) once daily. The best time to do this is in the evening' (underlining is Pfizers'). Pfizer Ltd UK state that : 'Xalatan is licensed for administration at night' (Letter from Pfizer UK- Appendix 2). A more specific time for administration is not designated. Early evening instillation should ensure increasing effects over the 6 to 12 hour period while the patient sleeps, maximising the dampening effect as well as eliminating the early morning spikes in pressure reported by Gelatt and MacKay (2001) and Zeimer *et al* (1990).

Further, if IOP peaks are predictable and can be related to sleep patterns, as this and other papers suggest, the administration of prostaglandin analogues could be customised to suit each patient's individual sleep pattern.

Final Statement

The results from this experiment lend further support that sleep related elevations in IOP exist. However more study needs to be done to confirm and investigate further the subtleties of the phenomenon, particularly how it relates to glaucoma sufferers of various ages. Significant advances in our knowledge will not be without a fundamental change in the methodological approach to the research.

Understanding the exact mechanisms for the rise in IOP noted during sleep could be vital in achieving elemental changes in the medical management of glaucoma. If a chemical mediator is identified its' actions must be equated to one of the three mediators of IOP homeostasis - aqueous influx, episcleral venous pressure and resistance to outflow.

Regardless of the factor or combination of factors causing the rise, current medical management should target sleep induced IOP peaks as well as mean or daytime measurements. The selectively timed administration of prostaglandin analogues gives us such a clinical tool.

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APPENDIX 1
Definitions of Terminology of Cyclic Rhythms

Circadian

A biological activity with a periodicity of 24 hrs that is independent of environmental variation.
www.dddmag.com/scripts/glossary.asp

Circadian means being, having, characterized by, or occurring in approximately 24 hour periods or cycles; in relation to sleep cycles.
neurolab.jsc.nasa.gov/glosscd.htm

— a term introduced in the 1950s, meaning of approximately 24-hour duration, which comes from the Latin circa (about) and dies (day)
www.hhmi.org/biointeractive/museum/exhibit00/glossary.html

taken from the Latin words meaning "around" and "day"
www.portfolio.mvm.ed.ac.uk/studentwebs/session1/group9/glossary.htm

of or relating to biological processes occurring at 24-hour intervals; "circadian rhythms"
www.cogsci.princeton.edu/cgi-bin/webwn

Diurnal

having a daily cycle or occurring every day; "diurnal rhythms"; "diurnal rotation of the heavens"; "the diurnal slumber of bats"
www.cogsci.princeton.edu/cgi-bin/webwn

Active during the daytime. Daily.
www.pestmanagement.co.uk/library/gloss_d2.html

Daily; related to actions which are completed in the course of a calendar day, and which typically recur every calendar day (e.g., diurnal temperature rises during the day, and diurnal falls at night).
www.erh.noaa.gov/er/pit/branick2b.html

Pertaining to the daylight portion of the 24-h day.
www.hardydiagnostics.com/Glossary-D.html

Daily; related to actions which are completed in the course of a calendar day, and which typically recur every calendar day (e.g., diurnal temperature rises during the day and falls at night).
meted.ucar.edu/mesoprim/glossary.htm

Recurring every day or having daily a daily cycle.
sol.crest.org/renewables/SJ/glossary/D.html

Daily. Of, or belonging to, the daytime.
education.qld.gov.au/tal/kla/compass/html/gloss.htm

Throughout the day, daily.
www.sciencemaster.com/physical/item/solar_glossary.php

, Having a daily cycle, or recurring every day.
www.lunarrepublic.com/info/glossary.shtml

Nocturnal

Active at night time as opposed to during the day
www.bpca.org.uk/glossary.htm

Related to nighttime, or occurring at night.
www.erh.noaa.gov/er/pit/branick2c.html

Pertaining to the dark portion of a 24h day; active at night (filariasis).
www.hardydiagnostics.com/Glossary-N.html

"Of the night;" pertaining to events happening during sleep or the hours of darkness.
www.sleepnet.com/definition.html

Of, or relating to, or occuring at night.
www.santacruz.k12.ca.us/~jpost/projects/OSP/glossary.html

Nyctohemeral

Both daily and nightly.

Synonym: nycterohemeral.

Origin: nycto-+ G. Haemra, day

Synonym: nyctohemeral.

Origin: G. Nykteros, by night, nightly, + haemra, day

APPENDIX 2.
Letter from Pfizer Global Pharmaceuticals

Pfizer Limited
Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS
Telephone: (01304) 616161

Medical Information Direct Line: Tel: 01737 331111
Fax: 01737 332507

Pfizer Global Pharmaceuticals

3 December 2004

Mr Peter Frampton
Aaron Optometrist
Bellway House
Woodhorn Road
ASHINGTON
Northumberland
NE63 0AE

Reference No: GD/041110/1862

Dear Mr Frampton

I am writing in response to your enquiry concerning our product XALATAN™ (latanoprost). You requested information regarding time of day dosing.

Xalatan is licensed for administration at night (1). Dose ranging studies and the phase III trial in Sweden demonstrated that a better control of intraocular pressure (IOP) is obtained if the product is given at night (2, enclosed). However, I also enclose details of a study which looked at morning administration (**unlicenced use**) (3).

Please do not hesitate to contact me if you require anything further.

Yours sincerely

Geraldine Dodd BSc (Hons)
Senior Medical Information Executive

References: (enclosed)

1. Xalatan Summary of Product Characteristics
2. Alm A et al (1995) Ophthalmology 102: 1743-1752
3. Racz P et al (1996) Arch Opthal 114: 268-273

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ

APPENDIX 3.
Patient Information and Consent Form

Study Title
'Diurnal variations in Intra Ocular Pressure, and the over riding effects of sleep. Implications with the single administration of prostaglandin analogue drugs for the control of glaucoma.'

Participation
You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. You may contact me, Peter Frampton, at the above address if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you.

Purpose of the study.
Fluid pressure inside the eye is recognised to fluctuate during the day, although the exact pattern of this fluctuation is not agreed.
Glaucoma is an eye disease caused by adverse levels of pressure within the eye. The treatment is to endeavour to reduce the pressure to a safe level. Previous medical treatments (eyedrops) for glaucoma have needed drops to be instilled at least twice per day. A recent addition to the medical treatment is a new group of drugs called prostaglandin analogues. These need to be instilled only once per day. These drugs appear to be most effective when instilled in the evening, however there is little understanding as to why this would be the case. If, as is suggested by this study, pressure peaks are expected during sleep then this would support the instillation of these drugs just prior to sleep. It may even be suggested that administration be customised to suit each patient's sleep pattern.

The study is designed to record the pressure inside the eye over a 24 hour period in a group. This group will remain awake during the day and will be encouraged to do any normal daily activities that do not stop them having their eye pressures recorded at the appropriate times. Sleep times will be up to the individual but it is hoped that most subjects will sleep at some time during the measurement period. Expected is a pressure peak during the sleep period.
A single information collection period is anticipated and the candidates will not need to return.

Why have I been chosen?
The study of the daily pressure changes occur in healthy individuals as well as people with glaucoma. Since we are studying the nature of the variation we do not need glaucoma patients. Healthy individuals such as yourselves are excellent candidates.
To make collection of measurements quicker it is easier to get a group of individuals who are willing to live together in close proximity for the 24 or 30 hour period. Venture scouts are ideal as we have the group accommodation, bedding and activity regimes that can make the experiment interesting and fun.

Do I have to take part?
It is up to you to decide whether to take part or not. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part will not be questioned or held against you by the researchers or the scout group.

What will happen to me if I take part?

All candidates will have a preliminary eye examination at the optometry practice. This will be to ensure eye health before the study. It will also give you a chance to ask any questions and to see the equipment we will use during the actual study.
The actual information collection will be done as a group at a scout accommodation, and probably over a Friday/Saturday. Your scout leader, Grant Watson, will liaise with you and the scouts will specify the most appropriate time and place.
The study period will commence at 0800 on day 1 with all participants having their eye pressures recorded with a Pulsair Non Contact Tonometer. An average or five readings per eye per measurement will be recorded. The pressure of the right eye only will be recorded. This is because the pressures between eyes is related and so recording both eyes will not give any extra information, but will take extra time. This is particularly important during the sleep periods when we are trying to disrupt sleep patterns as little as possible.
Pressure will be recorded hourly during awake periods and two hourly during sleep.
During the awake time normal activities will be arranged by the scout leaders, but we will also supply TV and DVDs.

The instrument used to record pressure blows a puff of air onto the front of the eye. No drugs or direct eye contact is needed. The high frequency of recordings is possible because this machine does not cause any adverse effects on the eye and can be repeated as often as required. You will get to handle the instrument at the initial eye examination to ensure you are happy with the process and to reassure you of its ease of use.

What do I have to do?

Lead as normal a daily life as is possible within the confines of the camp area. No drinking of alcohol or smoking is allowed as both these can affect eye pressure.
Hopefully you will enjoy the activities during the 24 or 30 hours.

Side Effects?

There are no side effects of the pressure recording technique used. It can be used as often as required with no adverse effects.

Possible disadvantages or risks of taking part?

If you have a disease or condition that does not allow you to have a disrupted sleep pattern or to sleep in scout hut conditions then you should not take part. If you need easy access to medical help for a medical problem and do not feel this would be as easy in a camp setting then you should not take part. Otherwise there are no risks during the study period.
If during the initial eye examination an otherwise unknown visual problem is detected then this will be discussed with you and a carer if appropriate in strictest confidence. You will be treated as any existing patient with full advice. No treatment or onward referral will be undertaken without your informed consent and all possible options and freedom of choice will be afforded.

Possible benefits of taking part?

A full eye examination is always recommended at routine intervals. If you have not had an eye examination recently or ever then it would be beneficial.
The findings of the study may benefit glaucoma suffers but will not benefit the study candidates who are being chosen as healthy individuals.

After data collection?

The candidates are free of commitment to the study once the single information collection period is over.
The information collected will be statistically analysed and the results presented as part of a masters degree in optometry at Bradford University.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. The scouts will have their normal insurances in place for general accidents.
Regardless of this, if you wish to complain, or have any concerns about the professional side of the study, rather than general safety, then you can lodge complaints through the normal optometry complaints procedure.

Confidentiality

All information collected during the research will be kept in strictest confidence. Any information about you will not carry your name.

Results

The results will be part of a Masters research topic at Bradford University. The finished paper should be submitted by September 2005. No participant will be named in the paper.
A copy will be kept at Aaron Optometrists, Bellway House, Woodhorn Road, Ashington NE63 0AE and anyone participating in the research is welcome to examine the paper.
If the results are worthy of publication you will be notified via Grant Watson of the journal and how to access it if required.

Funding

The research is being organised by Peter Frampton from Aarons with research supervisor Dr Niall Strang from Optometry Department, Bradford University.
It is being funded totally by Peter Frampton.

Ethics

Ethics approval was sort from Northumberland Local Research Ethics Committee.

Contact

For more information please contact Peter Frampton at Aaron Optometrists, Bellway House, Woodhorn Road, Ashington, NE63 0AE tel : 01670 813185

Thank you very much for considering this research project and I appreciate your time and commitment.

CONSENT FORM

Title of Project:
'Diurnal variations in Intra Ocular Pressure, and the over riding effects of sleep. Implications with the single administration of prostaglandin analogue drugs for the control of glaucoma.'

Name of Researcher:

Peter Frampton
Aaron Optometrists
Bellway House
Woodhorn Road
Ashington
NE63 0AE
01670 813185

Supervisor

Dr Niall Strang
Optometry Department
University of Bradford
West Yorkshire
BD7 1PD
01274 234640

Please initial box

1. I confirm that I have read and understand the information sheet the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my research records may be looked at by responsible individuals from Bradford University where it is relevant to my taking part in research. I give permission for these individuals to have access to my research records. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Signature	Date
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Signature	Date

1 for patient; 1 for researcher; 1 to be kept with hospital notes

APPENDIX 4.

Letter from Northumberland Local Research Ethics Committee

Northumberland Local Research Ethics Committee

Merley Croft
Loansdean
Morpeth
Northumberland
NE61 2DL

Administrator: Mrs Ann Young
Tel: 01670 394460
Fax: 01670 394501

19 March 2003

Mr P Frampton
Aaron Optometrists
Bellway House
Woodhorn Road
ASHINGTON
NE63 0AE

Dear Mr Frampton

NLREC 64/2002 Diurnal Variations in Intra Ocular Pressure, and the overriding effects of sleep. Implications with the single administration of prostaglandin analogue drugs for the control of glaucoma

Thank you for your letter of 26 February clarifying the issues raised at the February meeting on your study.

There was one point not covered in your letter and that was the indemnity for the study. I understand there is a problem obtaining policy details from the AOP but it is possible for you to get a copy of a letter from the AOP outlining the cover for the research. If this is how you propose to indemnify the study this will be sufficient for the ethics committee.

Once I have this information and a letter of support from the R & D at the Care Trust I will be able to issue the final approval letter.

Yours sincerely

MRS A YOUNG
LREC Administrator

APPENDIX 5
How Many Pulsair Readings are Appropriate?

The Keeler Pulsair 3000 instruction manual recommends accepting the mean of four successive readings as the IOP. Noncontact, air tonometers register a reading in 1 to 3 msec, corresponding to one five hundredth of the cardiac cycle (Piltz, Starita, Miron & Henkind 1985), making an average of a number of readings necessary to minimise variability attributable to the ocular pulse (Moses & Arnzen 1983, Moseley *et al* 1989). This technique may still not sample the full range of instantaneous tensions within the cardiac cycle (Piltz *et al* 1985) and methods to enhance accuracy have been suggested and used in research.

Reference to the documented acceptable margin of error when comparing tonometers of ±3 mmHg, is made by several groups of researchers (Evans & Wishart 1992, Kao, Lichter, Bergstrom, Rowe & Musch 1987, Mosley *et al* 1993, Shields 1982). These authors suggest taking consecutive readings until the required number (4 for the Pulsair 3000) fall within a 3mmHg range.

Moseley *et al* (1993) and Vernon (1995) found that an initial Pulsair 2000 reading was significantly higher than subsequent exposures, suggesting that the first should be discarded. Vernon attributed this phenomenon to anxiety of the patient with an unfamiliar technique. In this experiment the effect would only bias the very first recording of the day and would not affect subsequent exposures during the 24-hour collection period.

In normal use the Pulsair 3000 LED reading is the average of the measurements for that eye; only the initial reading constitutes a ‘true’ measurement, with all subsequent displays representing an average of all measurements. The instrument also measures to one decimal place during the series of measurements but gives a single averaged reading to the nearest whole number (Pulsair 3000 user manual 2001).

To take a series of individual readings, accepting the first four to fall within a 3mmHg range as suggested by Evans and Wishart (1992), Kao *et al* (1987), Moseley *et al* (1993) and Shields (1982) would have necessitated resetting the machine after each measurement. While allowing the elimination of spurious readings, this technique would have been significantly more time consuming and potentially disruptive. Further, the final recorded tension would have been the average of whole number measurements and not an average of readings to one decimal place.

Moseley *et al* (1989) suggested 5 consecutive readings are necessary to ensure adequate accuracy, while Vernon and co workers (1991) stress that at least four are required to maximise both sensitivity and specificity of referral. McCaghrey and Matthews (2001) found, with the Pulsair 3000, that three consecutive readings were adequate, to ensure repeatability of the measurement technique with 96% of readings falling within 1 mmHg of the stated machine standard.

Recording five instantaneous readings as suggested by Mosley and co workers (1989) was considered the most appropriate in these experimental conditions since it appears to maximise accuracy and repeatability while minimising sleep disruption.

APPENDIX 6.

Statistical Calculations

Summary of the data — **Statistics**

Subject	Sleep	Averages Awake	Averages Asleep	Difference	Y Awake-mean	X Asleep-mean	(X-Y)^2
1							
2							
3							
4							
5	G2	18.25	18.5	0.25	3.899256578	-3.23809524	50.9417781
6	G2	17.4	20	2.6	3.049256578	-1.73809524	22.91872879
7	G2	16.662	22	5.318181818	2.33107386	0.261904762	4.261460756
8	G3	16.391	28	11.60869565	2.040560026	6.261904762	17.81975138
9	G3	17.389	24	6.611111111	3.038144567	2.261904762	0.602548235
10	G3	13.833	21.3333	7.5	-0.51741099	-0.4047619	0.012689816
11	G3	12.5	22.5	10	-1.85074432	0.761904762	6.825935235
12	G3	13.333	24	10.66666667	-1.01741099	2.261904762	10.75391179
13	G3	10.667	21.3333	10.66666667	-3.68407766	-0.4047619	10.75391179
14	G3	13.85	18	4.15	-0.50074432	-3.73809524	10.48044095
15	G3	16.389	22.6667	6.277777778	2.038144567	0.928571429	1.231152549
16	G3	19.048	27	7.952380952	4.696874726	5.261904762	0.319256942
17	G3	13.905	24	10.0952381	-0.44598242	2.261904762	7.332652975
18	G3	12.294	20	7.705882353	-2.05662667	-1.73809524	0.101462276
19	G3	12.85	23	10.15	-1.50074432	1.261904762	7.632229961
20	G2/G3	11.789	19	7.210526316	-2.56127064	-2.73809524	0.031266939
21	G3	13.9	21.5	7.6	-0.45074432	-0.23809524	0.045219633
22	G2/G3	13	19	6	-1.35074432	-2.73809524	1.924742565
23	G2/G3	12.667	17	4.333333333	-1.68407766	-4.73809524	9.327023396
24	G3	16.111	22.3333	6.222222222	1.760366789	0.595238095	1.357524873
25	G3	9.1176	21.3333	12.21568627	-5.23309726	-0.4047619	23.31282233
			Mean diff	7.387350916			

Paired t-test:

Paired t-test using R statistical programme

Mean asleep	21.7361	T	11.0419
Mean awake	14.3507	d.o.f.	20
Sum Squared difference	188.007	p-value	5.89E-010
d.o.f. N(n-1)	380	True mean is between	5.991 8.782
T	10.5025	at the 95% confidence level	
T for 19 d.o.f.	P=0.05 2.09302		
	P=0.01 2.86094		

Histogram of differences: with right hins distribution approx. normal

Bin	Count
0-2	1
2-4	1
4-6	4
6-8	8
8-10	1
10-12	6
	21

Bin	Count
0-3	2
3-6	4
6-9	8
9-12	6
12-15	1
	21